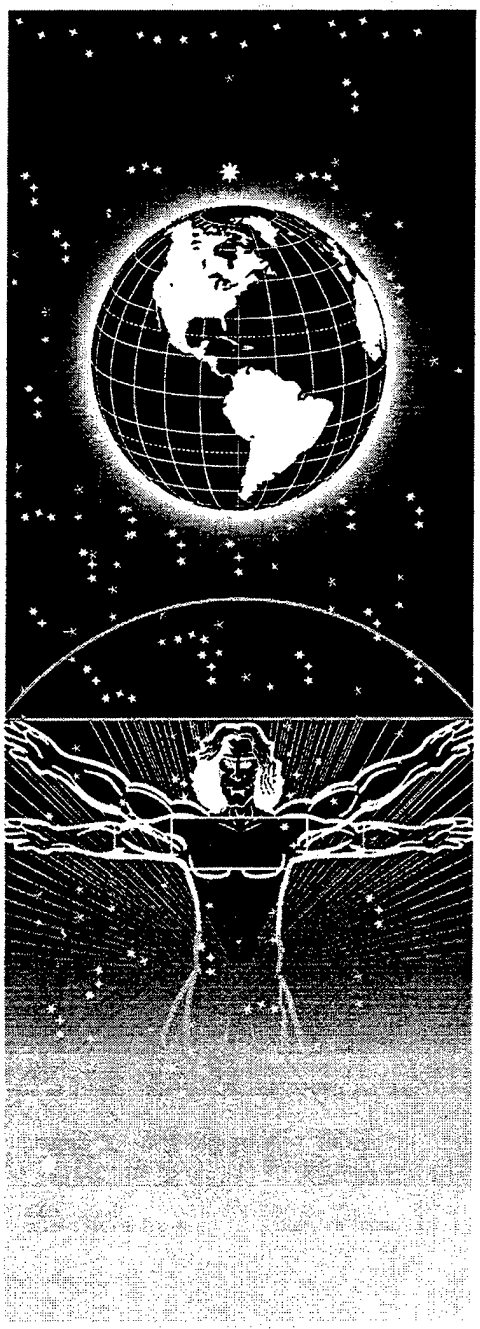
SAM-AF-BR-TP-1998-0001



UNITED STATES AIR FORCE
SCHOOL OF AEROSPACE MEDICINE

Lisinopril for the Treatment of Hypertension in Aviators

David B. Rhodes, Lieutenant Colonel, USAF, MC
Brian Howe

February 1999

USAF School of Aerospace Medicine
Clinical Sciences Division
2507 Kennedy Circle
Brooks AFB, TX 78235-5117

NOTICES

When Government drawings, specifications, or other data are used for any purpose other than in connection with a definitely Government-related procurement, the United States Government incurs no responsibility or any obligation whatsoever. The fact that the Government may have formulated or in any way supplied the said drawings, specifications, or other data, is not to be regarded by implication, or otherwise in any manner construed, as licensing the holder or any other person or corporation; or as conveying any rights or permission to manufacture, use, or sell any patented invention that may in any way be related thereto.

The mention of trade names or commercial products in this publication is for illustration purposes and does not constitute endorsement or recommendation for use by the United State Air Force.

The Office of Public Affairs has reviewed this report, and it is releasable to the National Technical Information Service, where it will be available to the general public, including foreign nationals.

This report has been reviewed and is approved for publication.

Government agencies and their contractors registered with Defense Technical Information Center (DTIC) should direct requests for copies to: Defense Technical Information Center, 8725 John J. Kingman Rd., STE 0944, Ft. Belvoir, VA 22060-6218.

Non-Government agencies may purchase copies of this report from: National Technical Information Services (NTIS), 5285 Port Royal Road, Springfield, VA 22161-2103.

David B. Rhodes MD

DAVID B. RHODES, Lt Col, USAF, MC, FS
Chief, Clinical Research Coordination Branch

DOUGLAS J. IVAN, Col, USAF, MC, CFS
Chief, Aeromedical Consultation Service

RODGER D. VANDERBEEK, Col, USAF, MC, CFS
Commander

REPORT DOCUMENTATION PAGE	Form Approved OMB No. 0704-0188

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	February 1999	Final, November 1992-March 1998

4. TITLE AND SUBTITLE
Lisinopril for the Treatment of Hypertension in Aviators

5. FUNDING NUMBERS
PE: 8224F
PR: 7755
TA: A0
WU: 07

6. AUTHOR(S)
David B. Rhodes, MD MPHTM
Brian Howe, MS

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
USAF School of Aerospace Medicine
Clinical Sciences Division
2507 Kennedy Circle
Brooks Air Force Base TX 78235-5117

8. PERFORMING ORGANIZATION REPORT NUMBER
SAM-AF-BR-TP-1998-0001

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION AVAILABILITY STATEMENT
Approved for public release; distribution is unlimited.

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

Hypertension affects 1% of USAF aircrew. Pharmacologic treatment options in the USAF have been limited to diuretics. Lisinopril is an angiotensin converting enzyme (ACE) inhibitor shown it to be safe and effective for treatment of hypertension with minimal side effects. Methods: Ninety-four aviators with essential hypertension were evaluated. Testing included audiologic, vestibular, ophthalmologic, laboratory and G-tolerance testing as well as coronary artery disease (CAD) screening. Results: There were no significant abnormalities detected which were directly attributed to lisinopril. Echo abnormalities were found in about 30% and led to disqualification in three aviators. Twenty-four aviators underwent cardiac catheterization due to positive noninvasive tests and 13/24 had gradable disease. G-tolerance was not significantly decreased in the 22 aviators who underwent centrifuge testing assessed by comparison to control group of normal aviators. Test results were used to construct an algorithm approach to local evaluation. Conclusion: The extensive central evaluation done on these aviators failed to detect aeromedically significant side effects associated with lisinopril for the treatment of essential hypertension. With the exception of G-tolerance testing for high performance aircraft aviators, all other testing necessary for initial and subsequent annual examinations can be done at the local level.

14. SUBJECT TERMS	15. NUMBER OF PAGES
Hypertension Lisinopril ACE inhibitor USAF aviator drug therapy	102
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
UNCLASSIFIED	UNCLASSIFIED	UNCLASSIFIED	UL

THIS PAGE INTENTIONALLY LEFT BLANK

TABLE OF CONTENTS

TABLES

FIGURES

ABSTRACT

LISINOPRIL FOR THE TREATMENT OF HYPERTENSION IN AVIATORS
David B. Rhodes, MD, MPHTM, Brian Howe,MS;
Introduction: Hypertension affects 1% of USAF aircrew. Pharmacologic treatment options in the USAF have been limited to diuretics, which were approved for use with a waiver in 1969. Lisinopril is an angiotensin converting enzyme (ACE) inhibitor approved by the FDA in 1987 for the treatment of hypertension. Randomized double-blind studies have shown it to be safe and effective for the treatment of hypertension with minimal side effects. In 1994 the Aeromedical Consultation Service (ACS) began a study to determine if lisinopril could be used safely in aircrew. This study sought to determine what sort of evaluation was necessary for the use of lisinopril in USAF aircrew. Methods: Ninety-four aviators with essential hypertension were evaluated at the ACS between November of 1992 and March of 1998. The protocol tested six areas felt to be potential problems for an aviator with hypertension and treated with lisinopril. These six areas were audiologic, vestibular, ophthalmologic, coronary artery disease (CAD) screening, laboratory testing and G-tolerance. Aviators were seen annually to follow the potential development of side effects over time. Results: There were no significant abnormalities detected which were directly attributed to lisinopril. Test results were used to determine the content of a local evaluation. Lab abnormalities were most often borderline changes not considered clinically or aeromedically significant, but did justify the use of lab testing and in some cases could have been due to lisinopril. None of the mild abnormalities resulted in discontinuation of lisinopril. Echo abnormalities were found in about 30% and led to disqualification in three aviators. Cardiac catheterization (cath) resulted from either an abnormal exercise treadmill test (ETT), coronary artery fluoroscopy (CAF), or thallium scintigraphy. Twenty-four aviators underwent cath and 13/24 had gradable disease. There were a total of 10 aviators disqualified for (aeromedically) significant coronary artery disease (SCAD) with 3 found to have minimal coronary artery disease (MCAD). This amounted to 13 out of 94 aviators screened (13.7%) with gradable CAD. G tolerance was not significantly decreased in the 22 aviators who underwent centrifuge testing assessed by comparison to a control group of normal aviators. Since there was no pre-lisinopril centrifuge testing done, the conclusion that lisinopril does not affect G tolerance must be viewed with some caution. Those who had successive annual examinations did not show any new side effects over up to four visits. One aviator failed to be controlled on even the maximum dosage of lisinopril (80 mg/d) and was disqualified, but otherwise all aviators had adequate control of hypertension on lisinopril. Conclusion: The extensive central evaluation done on these aviators failed to detect aeromedically significant side effects associated with lisinopril for the treatment of primary hypertension. The presence of abnormalities detected on the testing was used to construct an algorithm approach to the local evaluation of USAF aviators, which includes lab, echo, ECG and CXR. With the exception of G-tolerance testing for high performance aircraft aviators, all other testing necessary for initial and subsequent annual examinations can be done at the local level. The high percentage of aviators with gradable CAD necessitates a CAD screening program for aviators with hypertension.

THE RESULTS OF THE LISINOPRIL STUDY

INTRODUCTION

A study to determine the waiver requirements for aviators taking lisinopril to control essential hypertension has been completed. The results of that study have led to the development of new guidelines for the local initial work-up and follow-up of aviators treated for hypertension. This paper will present the pertinent findings of that study as they relate to the algorithm approach included here as attachment 1. This paper will also serve as the recommendation that no further initial lisinopril evaluations will be sent to the ACS, but instead will be completed by the local flight surgeon according to the guidelines presented in Attachment 1.

The U.S. Air Force has been granting waivers to aviators for the treatment of hypertension since 1969 [30]. The only class of drugs that was approved at that time for treatment of hypertension was the thiazide diuretics. The use of thiazide diuretics was based upon studies conducted with chlorothiazide at the USAF School of Aerospace Medicine (USAFSAM) at that time.[30,53] Since 1969, aviators have been allowed to have a local evaluation for hypertension and, if necessary, be treated with thiazide diuretic. A waiver could be obtained at the MAJCOM level. Triamterene was added as well as combination drugs with both hydrochlorothiazide and triamterene since that time based on the assumption that findings with thiazides could be extrapolated to other mild diuretics[23].

In 1972, USAFSAM published a study regarding the treatment of hypertension in aviators with Aldactazide[24]. This was a pre and post study that was done in 32 U.S. Air Force aircrewmen with mild or moderate uncomplicated high blood pressure. Using Aldactazide they were able to achieve good blood pressure control in 94% of those treated. Eighty-four percent were able to return to flying status. The conclusion of the study was that Aldactazide was a safe and effective second-line treatment for hypertension; however, it was never approved for treatment due to later findings of increased cardiac irritability on treadmill testing with aviators on Aldactazide[21]. However, this study was significant in that it demonstrated a technique whereby a medication could be evaluated with pre- and post testing at a central location.

Although thiazide diuretics were excellent drugs for the treatment of hypertension, it was found that there was some aircrew who did not tolerate the drug or their blood pressure was not controlled. In 1990, the Air Combat Command estimated that they had 55 aviators with poor control on thiazide diuretics. Moreover, Air Force-wide there was an estimated 200 aviators who could benefit from a treatment with a second drug for hypertension. Clearly there was a need for another drug to treat hypertension.

SELECTION OF LISINOPRIL

The challenge was to introduce a protocol which could provide data showing that the selected drug had no adverse effects on flying duties and yet would yield a work-up that

could be performed at the local flight surgeon's office. The main benefit of local evaluation is that it avoids the travel costs associated with sending the aviator to a central location, as well as increased expediency of the evaluation. Although the original data collection with lisinopril occurred at Brooks AFB, the ultimate goal was to design a strategy that could be operated at the level of the local flight surgeon.

The problems with selecting an additional antihypertensive medication for aircrew that would be effective as well as compatible with the aviation environment were reviewed by Hull in his article on mild hypertension in 1985[23]. At that time many of the newer drugs had not yet been introduced. Selection of lisinopril as a medication for aviators came only after careful consideration of the available anti-hypertensive drugs in the early 1990's.

Lisinopril is one of the antihypertensive medications that belong to the ACE Inhibitor group. It is a long acting drug that in most cases need only be taken once a day. It was approved for use in the US by the FDA in 1987 and has been shown to be safe and effective for the treatment of mild to moderate hypertension.[35] Side effects are uncommon and usually do not result in discontinuation of the medication.[35]It has been widely used for that indication since that time with many double-blinded control studies attesting to both its safety and its efficacy.[7, 20] Amroliwalla[4] has also recently reviewed its use in aircrew with the conclusion based on multiple studies that it is safe and effective in certain categories of aircrew.

In 1994 the Surgeon General of the Air Force approved a protocol to determine the waiver requirements for rated USAF aviators placed on lisinopril for the treatment of hypertension. The protocol was derived after consultation with experts in each system potentially affected by the drug or by hypertension itself. Pre-testing was considered in the initial process of designing the study but was deemed logistically untenable in this group of actively flying aviators. Pre- and post-testing, would have been the best means of determining if a discovered abnormality was due to lisinopril. A control group was also considered, but to get a similar group of aviators to undergo such detailed testing which could potentially threaten their job if an asymptomatic abnormality was incidentally found precluded this approach. The design arrived at takes into account these restrictions and yet provides useful information concerning the detailed follow-up of both the disease and of the treatment used to control the disease. Where it was feasible to do so, external controls consisting of similar populations of normotensive aviators were used as comparison groups. The protocol required aviators to complete a 30-day trial on lisinopril and to have adequate control of hypertension demonstrated with a normal five-day blood pressure average. Since 1994, 94 aviators have been evaluated according to this protocol at the Aeromedical Consultation Service (ACS) at Brooks AFB.

PROTOCOL FOR THE STUDY OF LISINOPRIL IN USAF AVIATORS

This observational study was designed to be a prospective cohort study. Most of the testing was compared to established norms rather than a separate control group derived from the same population. All aviators evaluated were seen with the first priority being to determine if they could be recommended for waiver. The needs of the study were secondary to this operational requirement. There was selection bias since only aviators

with hypertension best controlled with lisinopril were evaluated. Their blood pressure was treated and controlled at whatever dose was necessary up to a maximum of 80 mg/day by their local flight surgeon. Work-up for other associated abnormalities and tests to maintain that there were no side effects on lisinopril were all done at the local level.

Most of lisinopril's side effects are subjective and depend heavily on the treated person to reveal them to his physician. There was some speculation that a low incidence of side effects in aviators might not reflect a true picture of the side effect profile. Therefore, the investigators did attempt to provide some objective evidence that a particular side effect was not present with specialized tests of the vestibular system and visual system. The testing looked for side effects including dizziness and visual difficulties. Two of the tests lacked aviation or clinical standards; testing was performed to attempt to detect consistent abnormalities generated by persons on lisinopril. The neuropsychological tests, added later by the Surgeon General's office, also did not necessarily have a standard, but it was presumed that comparison to aviator norms would be sufficient. The centrifuge data utilized an external control group consisting of 434 normal aviators who had been evaluated on the centrifuge between the years 1977 and 1981[54]. Since both groups underwent a similar centrifuge protocol, the means for subcomponents of the centrifuge protocol could be compared from control group to lisinopril group. Differences in the means could then be assessed for significance with a t-test.

The other large area of testing was an assessment of each aviator's risk of coronary artery disease. This was done by performing screening tests for coronary artery disease on the aviators based on their age. All evaluees underwent treadmill exercise testing and those over age 35 had coronary artery fluoroscopy as well. Thallium scintigraphy was performed on aviators with an appropriate risk profile who also had an abnormal result on one of the preceding tests. The lisinopril protocol is included as attachment 2.

METHODS

Ninety-four aviators were evaluated at the Clinical Sciences Division of Armstrong Laboratory at Brooks Air Force Base, San Antonio, Texas, between November 1992 and March 1998, according to the protocol in attachment 2. The evaluation consisted of a complete history and physical examination and laboratory studies including electrolytes, BUN, creatinine, glucose, cholesterol, HDL cholesterol, triglycerides and calculations for the LDL and the ratio of cholesterol to HDL, calcium, phosphorus, complete blood count, PT, PTT, complete urinalysis, a TSH and a T_4 uptake. The evaluees also underwent a PA and lateral chest x-ray, and if they were over the age of 35 and male, they had coronary artery fluoroscopy performed. Blood pressure and pulse were performed on initial entry as well as weight, height and body fat determinations. Blood pressure readings were performed twice a day during the duration of their stay to obtain an average. A series of tests were performed that addressed six different areas of inquiry according to known side effects of lisinopril. Those areas were audiology testing, vestibular testing, visual testing, laboratory tests, and for those in high-performance aircraft, centrifuge testing. Cardiovascular testing included a resting ECG, exercise treadmill tolerance test according

to the USAFSAM modified Balke protocol, a holter monitor for approximately 18 hours, an echocardiogram and pulmonary function tests. All male aviators over the age of 35, as mentioned before, also underwent coronary artery fluoroscopy. If either the coronary artery fluoroscopy or the exercise treadmill tolerance test was abnormal, the aviator also had thallium scintigraphy. Generally, if any one of the three, either thallium, treadmill or coronary artery fluoroscopy was abnormal, the aviator underwent an aeromedical cardiac catheterization. This decision for cardiac catheterization was based on an assessment of risk of coronary artery disease with consideration of established risk factors. Audiology testing consisted of an audiogram. Vestibular testing consisted of eye tracking, both saccade and smooth pursuit, vestibular-ocular reflexes, and optokinetic testing. If there was asymmetry in the audiogram to a degree enough to cause concern for acoustic neuroma, a full audiometry evaluation including ABR and sometimes an MRI of the internal auditory canal was performed. If any of the above vestibular or audiology tests were abnormal, the aviator was usually seen by an otolaryngologist to determine the significance of the finding. The ophthalmology examination consisted of dilated fundus examination with photos if indicated, slit lamp examination, a refraction, depth perception testing, color vision testing, intraocular pressures, and visual field tests. They also underwent contrast sensitivity. As part of the occupational evaluation separate from the protocol, these aviators had IQ testing and a personality screen with an MMPI. In conjunction with this, they were also interviewed by a psychologist to determine the presence of any outstanding psychological problems.

STATISTICAL ANALYSIS

Each section of testing was analyzed separately. Most of the results were presented as rates of positive findings. In the areas where it was feasible to do so, an external control group was used to compare the results. For the lab data and pulmonary function tests, an age matched control group of aviators seen at the ACS for mitral valve prolapse (MVP) was used with a two to one ratio. For the centrifuge data, a control group previously utilized in a paper on MVP was used. Enhanced Flight Screening (EFS) data was used as a comparison for the MAB data. For the MMPI data there were two external control groups. There was data from a group of AFSOC applicants, and data from a group whose testing was used to establish aviator normative data for the MMPI. These groups are described in more detail under each data section. The means of each group were compared with a t-test to look for significant differences.

RESULTS

Results of this study will be presented in two major sections. The first section will deal with any of the findings that were not directly the results of a test. These are Demographics, Disqualifications, History, Physical Findings and Personal Habits. The second section will deal with the results of testing and will include: Audiometry, Vestibular testing, Laboratory tests, Ophthalmology testing, Cardiovascular testing, Centrifuge testing, and some limited psychological testing.

NON-TEST FINDINGS

Demographics

This group of 94 aviators included 91 males and 3 females. There were 87 Caucasians, 3 blacks, 1 Hispanic, and 2 Oriental. The mean age for the group was 41.7 years with a range from 28 to 55 years of age. The group included 50 pilots, 29 navigators, 14 flight surgeons and 1 other (weapons controller). Mean total flying hours was 2518 hours with a range from 0 to 7500 hours. The rank breakdown consisted of 19 colonels, 34 lieutenant colonels, 25 majors, 16 captains and no lieutenants. General officers were excluded from the protocol. The aircraft flown consisted of 30 considered high performance jets (F-16, F-15, A-10, etc.) and 61 considered aircraft of the TTB (transport, tanker, and bomber) category. Three persons had no specified aircraft. Table 1 shows the age breakdown for this group of aviators.

AGE RANGE	COUNT
20-29	3
30-39	29
40-49	55
50-59	7
TOTAL	94

Table 1 Age Distribution

Disqualifications

Of the 94 aviators evaluated, 18 were disqualified (19.1%), 2 received IIA waivers (one for MCAD and the other for mild aortic insufficiency (AI)) , 51 received IIC (no centrifuge) waivers and 22 received full FCII waivers after completion of a medically monitored centrifuge test. There was one aviator (a weapons controller) who received a FC III waiver. There was one FCIIB waiver for a 30% compression fracture of T-7 granted as part of a IIC waiver. All of those given IIC waivers were aviators who chose not to undergo centrifuge testing primarily because they did not fly high performance aircraft. Table 2 shows the breakdown of the disqualified aviators. There were no

DIAGNOSIS	NUMBER
SCAD	10
UNCONTROLLED HBP	1
PSYCHIATRIC	1
LVH	2
MCAD +VTACH	1
DECLINED CATH	1
PRIOR CONDITION	1
MODERATE TO SEVERE AI + VTACH	1
TOTAL	18

Table 2 Disqualifications

disqualifications directly attributable to lisinopril.

Of the 94 aviators, 10.6% (10) were disqualified due to the finding of SCAD. The definition and consequences of the diagnoses of SCAD and MCAD are discussed in greater detail elsewhere[8] but briefly SCAD is (aeromedically) Significant Coronary Artery Disease-a 50% or greater occlusion of any coronary vessel or a cumulative percent occlusion of more than one vessel of 120% or more. MCAD is Minimal Coronary Artery Disease and is single vessel disease of less than 50% or a cumulative percent of multiple vessels of less than 120%. Aviators with MCAD may receive a IIA waiver which permits them to resume flying duties, but only in non-high performance aircraft.

Two aviators were disqualified with left venticular hypertrophy (LVH).The "prior condition" listed in Table 2 was an acoustic neuroma. This aviator was sent to the ACS in the hopes of receiving a waiver for both conditions; on evaluation he was found to still have some residual symptoms from the surgery. The aviator who declined catheterization had a positive fluoroscopy for calcification in the proximal LAD. The psychiatric disqualification was due to depression. The aviator with "uncontrolled BP" was on the maximum dose of lisinopril (80 mg/day) and his blood pressure was still not adequately controlled. In addition, his creatinine had become elevated. He was switched to another anti-hypertensive medication that was non-waiverable. The combination of MCAD and ventricular tachycardia (V-Tach) is disqualifying, as is the combination of moderate to severe AI and V-Tach. Those disqualified for a complication of hypertension (SCAD, uncontrolled BP, LVH, MCAD + V-Tach, and declined cath) comprised 83% of the disqualifications, which points out the need for early identification and timely treatment of hypertension.

One of the aviators with SCAD had MCAD on his initial cath. As part of the protocol for MCAD he returned for a re-cath three years later which showed progression to SCAD. He was disqualified from flying duties at this point. One aviator disqualified for SCAD had the onset of chest pain a year and a half after the disqualification and had to have bypass surgery done for a lesion in the LAD which progressed from 70% to 95% over that time interval.

The testing which led to a disqualification included echo, treadmill, and CAF. There was one disqualified as a result of depression confirmed on psychological testing, but this was picked up by the examining flight surgeon on history and physical. There was also a single case of V Tach on holter monitoring, but in this particular case, moderate to severe AI, picked on echo, also had an impact on the aviator's disposition. The point of this discussion is these tests should be considered in the work-up of aviators with hypertension; they were the tests used to select out the majority of the disqualifications.

History

Findings on the history included the circumstances surrounding the selection of lisinopril, the duration of the hypertension, work-up for secondary hypertension and other

medications. Of the 94 aviators, 61 (64.9 %) had been on thiazide diuretics prior to the initiation of lisinopril. The reason for discontinuing the thiazide to switch to lisinopril was most commonly (54%) failure of the thiazide to control the blood pressure despite maximal (and sometimes heroic) doses of the thiazide. Side effects from the thiazides were responsible for another 31%. These side effects included fatigue, frequent urination, headache, decreased libido, dizziness, increase in lipids, glucose or uric acid, gout, and one aviator with a reversible decrease in creatinine clearance. The remainder stopped thiazide in combination with an ACE inhibitor due to the fact that the combinations were not waiverable. Other medications used for hypertension were all non-waiverable and included enalapril, captopril, propanolol, atenolol, several calcium channel blockers, and several other brands of ACE inhibitors. All of these medications were discontinued due to the fact that they were incompatible with continued flying. Interestingly, 10 aviators had been controlled on the combination of an ACE inhibitor and a diuretic prior to being placed on lisinopril alone. Two were on lisinopril + HCTZ, three were on another ACE + HCTZ and five were on the combination of Maxide® plus lisinopril. The combination of an ACE inhibitor and a potassium-sparing diuretic is not recommended.

DOSE (mg/d)	NUMBER ON DOSE
2.5	2
5	12
7.5	2
10	29
15	4
20	29
30	4
40	9
60	1
80	2
TOTAL	**94**
MEAN	**18.19**

Table 3 Dosage of lisinopril

Side Effects Seen With Lisinopril		
Side Effect	Number	Per Cent
cough	8	8.50%
lightheaded (1st week)	2	2.20%
transient mild increased K, BUN	1	1.10%
diarrhea	1	1.10%
weight gain (from stopping thiazide)	1	1.10%
photosensitivity (1st week)	1	1.10%
occasional fatigue	1	1.10%
increased sweating	1	1.10%

Table 4 Side Effects

A work-up for secondary hypertension was documented in 17 aviators. None of these were positive although there were two aviators with concurrent diagnoses involving the kidney. One had polycystic kidney disease (PKD) and the other had a history of mild glomerulonephritis. There were four aviators who did in fact have hypertension secondary to kidney disorders; they were not included in the study group due to the exclusion criteria of this study

Dosage of lisinopril ranged from 2.5mg/day to 80 mg/day. The mean dosage was 18.19 mg. The distribution of lisinopril dosage is shown in Table 3.

Side effects with lisinopril were rare, and were seen in 16 aviators in the distribution shown in Table 4. Eight had the dry cough characteristic of ACE inhibitors. The other side effects were only seen in one or two aviators and most were present only during the first one to two weeks of treatment. None of the aviators with the cough felt it to be severe enough to discontinue the lisinopril. Lab side effects will be addressed in the lab test section.

The length of time these aviators had a documented history of hypertension prior to being seen at the ACS was extremely variable and is shown in table 5. Many of these were found to have "borderline" or "white coat" hypertension and were not treated since they usually could pass a 5-day blood pressure check. Several also had at least one period of six months of non-pharmacologic treatment with diet and exercise. Thirty four per cent of these aviators were not treated until they were started on lisinopril. The others were usually treated with thiazide diuretics.

Years of Hypertension	Number
0.5 to 1.5	24
2 to 5	21
6 to 10	20
11 to 15	21
16 to 23	8
TOTAL	**94**

Table 5 Hypertension History

All aviators in this study were required to have a 5-day blood pressure average that was normal to be entered into this study. Although not all the records included this value, the majority did. The mean systolic for this group was 126.66 ± 5.33 (mean ± St Dev), with a maximum of 138 and a minimum of 115. The mean diastolic pressure was 80.21 ± 5.23 with a maximum of 88 and a minimum of 66.

Personal Habits

Diet history showed 69/94 (73%) on some kind of restricted diet. Primarily these were some combination of low-fat, low-salt diets. A low sodium component was found in the diets of 50% (35/69) of those aviators with a restricted diet. Some attempt to limit fats or cholesterol was found in 77% (53/69) of this group.

PACK-YEARS	NO. OF SMOKERS	YEARS QUIT	NO. OF SMOKERS
0-9	10	0-9	11
10-19	6	10-19	5
20-29	4	20-29	7
30 or Greater	3	30 or Greater	0
Unknown	2	Unknown	2
TOTAL	25	**TOTAL**	25

Table 6 Smoking History

Smoking history showed that only 3 were active cigarette smokers (3.2%). There was also one cigar smoker and one pipe smoker. There were 22 former smokers. The pack year history and the number of years since they last smoked are shown in Table 6.

Exercise

The majority of these aviators were on a regular exercise program. A breakdown of these is shown in Table 7. Many of these aviators were also on weight lifting programs in addition to their aerobic exercise.

AEROBIC EXERCISE HISTORY	
LEVEL OF EXERCISE	NUMBER
None	10
Less than 20-30 minutes 3X/wk	11
20-30 minutes 3X/wk	38
Greater than 20-30 minutes 3X/wk	35
TOTAL	**94**

Table 7 Exercise

Alcohol

The alcohol intake for this group of aviators is noted in table 8. This was the amount of beer, wine or mixed drinks that each aviator admitted to during the history. The majority of them had from "none" up to1 alcoholic drink per day on the average. Of the 26 that exceeded this amount, seven were found to have elevations of liver function tests, MCV or both. These elevations usually resolved with abstinence.

ALCOHOL INTAKE PER WEEK	NUMBER
None	9
Rare to 1/wk	20
2 to 3 /wk	23
4 to 7 /wk	16
8 to 14 /wk	17
15 to 48 /wk	9
TOTAL	**94**

Table 8 Alcohol

Family history

Seventy per cent of the aviators had a positive family history in a first degree relative for hypertension. Family history for coronary artery disease in a first-degree relative according to the NCEP guidelines[49] was positive in 26 out of 94 (26.6 %). Another 12 had indeterminate family history with a first degree relative with CAD, but the age of onset was uncertain. Fifty-six aviators had a negative family history for CAD.

Physical Exam

Most of the aviators examined had normal physical exams. About a third of the aviators had findings on the physical exam. None of the findings were related to the use of lisinopril but some were related to hypertension. There were nine with heart murmurs; two had previously documented MVP and one had severe AI. The other seven had no correlative findings on echo. Two others had an audible S4. One had borderline LVH on echo and the other had mild left atrial enlargement (LAE) without hypertrophy. Other findings unrelated to hypertension included a thyroid mass that was found (at the ACS) on examination (a Hurtle cell tumor), a symptomatic hydrocele requiring surgical repair, and 2 cases of psoriasis. There were no findings compatible with end organ damage on physical examination except for one with possible AV-nicking noted on the retinal exam. Twelve had various skin disorders unrelated to lisinopril and six had various GU disorders (hydroceles, spermatoceles, and varicoceles). The aviator with a known history of PKD had a palpable kidney on examination. Otherwise there were no findings to suggest a secondary cause for the hypertension.

The mean heart rate during initial physical exam at the ACS was 70.3 ± 12.2. The mean systolic blood pressure was 133.2 + 11.3 and the mean diastolic blood pressure was 84.1 + 9.3.

TEST FINDINGS

There was no concurrent control group for the many tests these aviators underwent as a part of this protocol, which made attributing any abnormality found to lisinopril difficult. To compound this problem, 34 (36.2%) of these aviators were on other medications including lovastatin, gemfibrozil or bile acid sequestrants for hyperlipidemia as well as Synthroid®, probenecid, allopurinol and Timoptic®. Six aviators took a total of three medications including lisinopril.

Audiometry

On audiometry there were 79 H1 profiles, nine H2 profiles and three H3 profiles. None of these hearing losses progressed as a result of treatment with lisinopril. Repeat testing on serial evaluations showed a progression from H1 to H2 in one aviator, H1 to H3 in two aviators and H2 to H3 in two aviators. In each of these cases there was no increase in hearing loss. The change in the profile was due to a change in the classification scheme for each of these profiles. No progression of hearing loss was noted. One interesting finding was that 17%(16/94) of this group of aviators had asymmetric hearing loss. One aviator was found to have asymmetric hearing loss at the local base during his initial

work-up for lisinopril treatment. The audiology and ENT work-up that ensued revealed the presence of an acoustic neuroma, which was subsequently removed.

Vestibular testing

Vestibular testing consisted of the VOR (Vestibular-Ocular Reflex testing), eye tracking tests (both smooth pursuit and saccade) and Optico-Kinetic (OPK) testing. There were a few who also had posturography testing as well.

The VOR showed some interesting but unrevealing results. The normal range for hypertensive individuals has not been established and work establishing the definitive range for abnormalities has only begun. There are no aviator standards for this test and there was no pre-testing of this group prior to treatment with lisinopril. There was no suggestion in the literature that lisinopril was an ototoxic drug. Using established means derived from a normal control group, a range of one standard deviation above and below the mean was used to separate normal from abnormal results. Using these criteria, 23.7% of the lisinopril group had some abnormality on VOR testing. Most were mild and none of these had vestibular symptoms or any outward manifestation of the abnormality (except the one with the acoustic neuroma). Out of the 22 aviators with abnormal findings, 12 had abnormalities of symmetry, 8 had gain abnormalities, and 14 had phase abnormalities (some had combinations of abnormalities). A right or left asymmetry might correlate with a prior vestibular insult that had since been compensated. Gain abnormalities correlate with the sensitivity of the vestibular system. Someone with a high gain might have a stronger tendency toward motion sickness. The phase is a measure of the comparison between the movement of the rotary chair and the corresponding movement of the eyes; it is perhaps the most stable parameter measured in the rotary chair testing [12]. Of the 31 aviators who had two or more evaluations, three showed a change from their initial test results. All three were abnormal on their first VOR and normal on their second test. In those with a deviation from the norm on the tests, ENT evaluation failed to reveal a specific defect, so in most cases the abnormalities were considered "neither clinically nor aeromedically significant".

Eye tracking also showed a variety of responses. This test had the same limitations noted for the VOR in regards to aircrew standards. Twenty-three per cent had mild abnormalities noted on smooth pursuit tracking, and 12.9% had abnormalities of saccade tracking. Of the 31 with repeated testing, two showed a change over time on the smooth pursuit testing and six showed a change over time on saccade testing. Both of the smooth pursuit changes were improvements from abnormal to normal. Of the six with changes on saccades, one improved, one changed from abnormal to normal and then back to abnormal, and the other four went from normal to abnormal. This test required the aviator to maintain attention to attain a normal result.

Posturography was performed on 14 of the evaluees. There were no abnormalities noted and testing was discontinued due to insurmountable difficulties with logistics.

OPK showed only one abnormal result, which was present in the aviator who had the surgery for the acoustic neuroma.

Vestibular testing on the whole did not reveal any abnormality that was disqualifying or symptomatic with the exception of the aviator with the history of an acoustic neuroma. None of the abnormalities could be attributed to lisinopril or to hypertension.

Ophthalmologic testing

Ophthalmologic testing included external exam, visual acuity, color vision, depth perception, fundus examination, lens exam, visual field testing, intraocular pressure measurement and contrast sensitivity. Fundus photos were taken for later comparison and documentation of any abnormalities found.

There were no non-waiverable disqualifications as a result of findings on the ocular exam. There were an abundance of ophthalmologic diagnoses made, but most of the additional findings were not deemed visually significant. There was a wide range of visual acuity decrements found, but all were correctable to 20/20 with spectacles.

There were four cases of color vision abnormalities. Two of these were felt to be congenital (one deuteranomalous, the other protanomalous). One had "weak" color vision and the other aviator had a tritan defect that was felt to be an acquired defect. The cause or the duration of this defect could not be ascertained, but it was doubtful that lisinopril caused it.

There were six aviators who had lenticular changes. Three of these were mild scattered opacities deemed visually insignificant. The other three were cataractous changes of the lens, a sector cataract of one eye, and one with an early nuclear cataract. None of these were thought to be caused by lisinopril. Mild depth perception problems were found in five aviators and another four had a diagnosis of ocular hypertension with or without pigmentary dispersion syndrome. Two of these were being treated with a topical beta-blocker. None had glaucoma. Eight were found to have cup to disc problems; all of these were insignificant. Other diagnoses included an old central retinal vein occlusion, a history of idiopathic central serous chorioretinopathy (ICSC), and a Roth spot, which was worked up locally.

Three aviators had findings on the dilated fundus exam felt to be secondary to hypertension. Two had old blot hemorrhages and one aviator had a cotton wool spot. There were no findings of arterial changes specifically noted by the ophthalmologist (e.g. arterio-venous nicking).

Contrast sensitivity did reveal a variety of results but this test, like the VOR, had no standards for aviators. A finding of significant loss of contrast sensitivity was present in 23% of the aviators. Of these abnormal findings, about 90% were asymmetric comparing right to left eye, and 30% showed one eye with abnormal contrast sensitivity with the other eye normal. This would hardly be the pattern for a drug effect. Another 29% of the aviators had "low normal" contrast sensitivity. This also frequently affected only one eye with the other eye having normal contrast sensitivity. Initial findings were consistent on retest in all but 12 of the aviators. Of these12, six got worse over time and three

improved. Two aviators who had three evaluations had a decrease in contrast sensitivity on their second evaluation that returned to normal on their third evaluation. The third one improved then returned to his previous loss. The abnormalities found did not relate to best corrected visual acuity nor was any abnormality of the visual axis found. There were a few who had concurrent ophthalmologic diagnoses that could account for the decrement in contrast sensitivity. One example would be the aviator with the early cataract. In none of these could the loss in contrast sensitivity be attributed to lisinopril. The significance of a decrease in contrast sensitivity in aviators is not known but a comment from the electrophysiologist interpreting this test was that there could be a decrease in visual acuity in low contrast conditions.

Laboratory testing

The routine lab tests for all lisinopril evaluees are shown in table 9. The liver function tests consisted of total protein, albumin, AST, ALT, GGT, alkaline phosphatase, LDH and bilirubin. The lipid panel consisted of total cholesterol, HDL cholesterol, triglycerides, and the calculated values of the LDL cholesterol and the cholesterol to HDL ratio.

Abnormalities were found in the frequency noted in table 10. Any abnormalities found were repeated or worked up as needed. In no case did they result in discontinuation of the lisinopril or modification of the dosage. The most significant abnormality found was mild elevations of the serum creatinine. Each time this was found, a 24-hour urine for

LABORATORY TESTS
CBC
Electrolytes
Liver Function Tests
Urinalysis
BUN
Creatinine
FT4
TSH
PT, PTT
FBS
Calcium
Lipid Panel

Table 9 Lab List

creatinine clearance was done and found to be within normal limits. Often, consultation with a nephrologist was also obtained. Follow up of these showed returns to the normal range in all cases. In one aviator, the creatinine went as high as 2.3 during his initial month of treatment. Lisinopril was discontinued and a work-up for renovascular hypertension was negative. The aviator was re-challenged with lisinopril and had no further elevations of the serum creatinine. Another aviator who had been disqualified for lack of control of his elevated blood pressure with the maximum dose of lisinopril (80 mg/d) was also found to have an elevated creatinine. Lisinopril was discontinued in this

aviator. Only 3 of this group had an elevated BUN. These were all borderline elevations that generally reverted to normal on retest.

Compared to an age-matched control group of aviators being evaluated for MVP, there were differences in the means noted in the tests shown in table 11. Where the p value was < 0.05, the table indicates in which direction the difference was for the lisinopril evaluees. All means for both groups were within normal range. It was interesting to note that neither the WBC, creatinine, nor the BUN showed any significant difference with lisinopril. The differences seen in the SGPT, the GGT, cholesterol and the ratio were all reflected in the percentage of abnormal tests seen in the lisinopril group. The LDL approached significance as well.

The hematocrit and the hemoglobin were abnormal in about 9% of the aviators. These abnormalities were borderline and usually were normal on retest. Small decreases in the hematocrit and hemoglobin have been reported with lisinopril but are rarely of any clinical importance[45]. The white blood cell count was often on the low side of normal in this group. In no case did the absolute neutrophil count fall below 1800 nor did any WBC

Lab Test	Frequency	Per Cent
HEMATOCRIT	9/94	9.58%
HEMOGLOBIN	8/94	8.50%
MCV	9/94	9.58%
WBC	12/94	12.70%
SEDIMENTATION RATE	8/94	8.50%
TOTAL PROTEIN	7/94	7.44%
ALBUMIN	17/94	18.06%
CHOLESTEROL, TOTAL	59/94	62.80%
HDL CHOLESTEROL	25/94	26.60%
TRIGLYCERIDE	16/94	17.02%
CHOL/HDL RATIO	61/94	64.90%
CALCULATED LDL	53/94	56.40%
ALT (SGPT)	20/94	21.30%
AST (SGOT)	9/24	9.58%
LD	8/94	8.50%
ALK PHOS - HITACHI	0/94	0.00%
TOTAL BILIRUBIN	26/94	27.65%
GGT	6/94	6.38%
URINE PROTEIN	one "trace"	N/A
UREA NITROGEN (BUN)	3/94	3.19%
CREATININE	6/94	6.38%
SERUM CALCIUM	0/94	0.00%
SODIUM	7/94	7.44%
POTASSIUM	0/94	0.00%
URIC ACID	8/94	8.50%
sTSH	2/94	2.13%
GLUCOSE - FBS	5/94	5.31%

Table 10 Frequency of Abnormal Lab Tests

count fall below 3400. On re-evaluation these low WBC counts usually returned to normal and in no case did they result in discontinuation of the lisinopril. There was no significant difference in the WBC mean for the matched group of MVP evaluees. Moreover, agranulocytosis, which has been reported for both captopril and enalapril, has not occurred with lisinopril.[35] The MCV was elevated in nine aviators, nearly always the result of alcohol overuse. The sedimentation rate was mildly elevated in 8.5% of the

	Lisinopril Initial Eval.					MVP Control Group							
Lab Test	Mean	Cnt	Min	Max	S.D.	Mean	Cnt	Min	Max	S.D.	t value	signif	p<.05
HEMATOCRIT	44.63	93	39.2	53.3	2.91	44.40	188	35.7	51	2.59	0.672	0.3021	
HEMOGLOBIN	15.40	93	13.4	17.7	0.96	15.31	188	12.5	18.1	0.93	0.755	0.4507	
RBC	4.99	93	4.01	6.01	0.39	4.94	188	3.84	6.02	0.35	1.080	0.2791	
MCV	89.59	93	77.8	99.3	3.97	89.73	188	81	99	3.76	-0.288	0.7733	
MCH	30.92	93	25.1	34.1	1.46	31.01	188	27.5	35	1.55	-0.476	0.6410	
MCHC	34.49	93	32.2	36	0.72	34.51	188	31.2	38	1.08	-0.200	0.8717	
WBC	5.94	93	3.4	10.2	1.31	5.85	188	2.6	11.5	1.51	0.491	0.6241	
NEUTROPHILS	57.32	93	42	75.4	7.91	49.89	188	28	73	8.70	6.940	0.0001	higher
BANDS	1.61	33	0	5	1.60	3.12	184	0	18	3.52	-2.420	0.0165	lower
LYMPHOCYTES	29.90	93	13.6	45.5	7.27	35.26	188	13	61	9.36	-4.830	0.0001	lower
MONOCYTES	7.14	93	0	13.3	2.91	4.95	188	0	25	3.13	5.630	0.0001	higher
EOSINOPHILS	2.87	93	0	11.4	1.94	2.85	188	0	12	2.23	0.074	0.9414	
BASOPHILS	0.38	93	0	4.1	0.56	0.05	187	0	2	0.24	6.890	0.0001	higher
SED RATE	8.03	90	0	238	25.05	5.63	187	0	32	5.63	1.250	0.2129	
TOTAL PROTEIN	7.38	94	6.5	8.8	0.45	7.17	186	1.9	8.3	0.55	3.200	0.0015	higher
ALBUMIN	4.37	94	3.8	5.3	0.28	4.40	180	3.7	5.8	0.34	-0.735	0.4630	
LD	163.74	93	105	565	85.21	133.81	188	66	212	26.93	4.400	0.0001	higher
CHOLESTEROL	207.80	93	130	307	37.43	199.39	188	117	318	35.81	-43.100	0.0001	higher
HDL CHOLESTEROL	43.40	93	23	106	12.58	44.74	188	14	90	12.25	-0.855	0.3932	
TRIGLYCERIDE	157.28	93	46	537	96.14	120.19	188	35	1848	138.19	2.320	0.0208	higher
CHOL/HDL RATIO	5.12	93	2.3	9.5	1.54	4.61	102	2	10.2	1.48	2.360	0.0194	higher
CALCULATED LDL	134.25	89	57	240	34.00	126.52	102	68	229	30.00	1.670	0.0967	
ALT (SGPT)	32.39	93	10	137	19.98	24.25	187	7	126	13.98	4.100	0.0001	higher
AST (SGOT)	26.62	94	13	218	22.65	23.10	188	0	92	9.25	1.850	0.0658	
ALK PHOS	74.06	62	32	126	19.23	55.86	129	24	175	18.23	3.990	0.0001	higher
TOTAL BILIRUBIN	0.95	94	0.4	2.4	0.37	0.81	187	0.3	2.4	0.34	3.160	0.0017	higher
DIR. BILI.	0.26	16	0.1	0.8	0.16	0.29	12	0.1	0.6	0.16	-0.491	0.0628	
GGT	35.47	85	9	197	31.00	26.84	76	7	149	23.08	1.980	0.0489	higher
SPECIFIC GRAVITY	1.02	94	1	1.031	0.01	1.02	187	1.002	1.035	0.01	1.070	0.2851	
pH	5.94	93	5	8	0.72	5.87	188	5	8	0.69	0.790	0.4305	
BUN	14.4	94	7	23	3.44	15.06	188	9	26	3.01	-1.630	0.1042	
CREATININE	1.2	94	0.8	1.7	0.19	1.19	188	0.9	1.6	0.14	0.516	0.6060	
CALCIUM	9.47	94	8.8	10.8	0.45	9.24	188	8.3	10.2	0.38	4.520	0.0001	higher
SODIUM	140.65	94	132	148	3.05	141.96	188	136	147	2.30	-4.030	0.0001	lower
POTASSIUM	4.31	94	3.5	5.5	0.35	4.28	188	3.2	5.5	0.41	0.627	0.5309	
TCO2	27.96	94	22	34	2.64	28.98	144	22	35	2.20	-3.230	0.0014	lower
CHLORIDE	104.12	94	93	112	2.93	103.34	175	94	110	3.22	1.950	0.0518	
URIC ACID	6.2	94	3.6	10.3	1.23	5.49	188	2.6	9.6	1.15	4.780	0.0001	higher
sTSH	2.19	90	0.2	16.1	1.89	1.95	76	0.4	6.3	1.23	0.950	0.3436	
PLATELETS	238.48	93	147	340	44.77	244.34	175	123	450	54.14	-0.894	0.3723	
PT	11.92	93	10.3	14.4	0.79	12.13	176	10.8	14.5	0.59	-2.430	0.0158	lower
GLUCOSE - FBS	99.47	94	80	122	8.42	96.27	188	72	128	8.14	3.080	0.0023	higher

Table 11 Lab Means: Lisinopril Group vs. MVP Group

aviators. One aviator also had mild myalgias. There was a syndrome noted in the PDR[45] of elevated sedimentation rate, myalgias, arthralgias, fever, vasculitis, rash, leukocytosis, eosinophilia, photosensitivity and positive ANA associated with lisinopril that is mentioned in the PDR[45]. This particular aviator was tested for this, but the ANA was negative, he had none of the other findings and over about one month his sedimentation rate returned to normal. His "myalgias" resolved in a few days. The cause of the increased sedimentation rate was not determined but it was not felt to be due to lisinopril.

The elevated total protein and albumin results seen were mild and usually transient in nature. A few were referred to their local flight surgeon for follow-up if they persisted on retest.

At least one of the transaminases was abnormal in 27 of the 94 aviators. Eighteen had isolated abnormalities of the ALT, the AST or the GGT. There was another 8 with elevated LD values, one of which had a concurrent mild elevation of the ALT. Each case was evaluated individually and in most cases these spontaneously reverted to normal on retesting despite no change in the lisinopril. Four aviators had elevations of all three transaminases and in addition two had elevated MCVs. These elevations were directly attributable to alcohol overuse and dropped to normal after a period of abstinence. Whether or not the elevations in the liver function tests were due to lisinopril was often difficult to determine due to the frequent contribution of other medications or alcohol

Borderline elevations of the bilirubin (1.1 to 1.5) were seen in 19 aviators, most of which reverted to normal on retest. There were four with elevations of the bilirubin due to Gilbert's Syndrome. There were no elevations of the alkaline phosphatase seen although the mean for the lisinopril group was significantly higher than that of the MVP control group.

Urinalysis showed no abnormalities, specifically there were no cases of proteinuria noted. In one case, "trace" protein was found which reverted to negative on retest. Other tests of significance included the sodium, potassium, uric acid, serum calcium and a fasting glucose. Although the mean of the serum calcium for the lisinopril evaluees was significantly higher than the mean for the MVP matched control, there were no calcium values above the normal range. There were 7 aviators with abnormal sodium values. Two were mildly elevated and 5 were mildly depressed. None were clinically or aeromedically significant. There were no abnormal potassium levels among this group of aviators. Uric acid was found to be elevated in 8.5% of the group. Half of these were borderline elevations and the other half were in the 10-11 mg/dl range. None of those with the higher range had a history of gout or uric acid kidney stones. One of those with a mild elevation had a history of gout but was not on treatment at the time of his evaluation. There were an additional four aviators with a history of gout who did take medication including probenecid and allopurinol; they all had normal uric acid values. Fasting glucose was elevated in 5 aviators. None were greater than 125 and three of the five were normal on repeat. The other two had follow-up with their local flight surgeon.

The sTSH was abnormal in two aviators. One was hypothyroid by history and was on synthroid. His level was elevated indicating possible undertreatment. He was referred back to his local flight surgeon. The other abnormal was also in an aviator on synthroid for suppression therapy. His level was borderline low.

The other major part of the lab testing was the lipid studies. This consisted of total cholesterol, an HDL cholesterol, serum triglycerides, calculated LDL and cholesterol to HDL ratio. Of this group, 63% had an abnormal cholesterol of 200 or greater (two were greater than 300) and 26% had an LDL of 160 or greater. An additional 30% had LDLs greater than 130. Five individuals had triglyceride levels greater than 400, which precluded calculating their LDLs; there were a total of 16 with elevation of the triglycerides. Another 26% had HDL less than 35, and 65% had a cholesterol to HDL ratio greater than 4.5.

Out of these 94 aviators with hypertension, 51 had a secondary diagnosis of hyperlipidemia for which 14 were on lovastatin, 9 were on a bile acid sequestrant (either cholestyramine or cholestid), one was on gemfibrozil and the rest were on diet treatment.

Radiology

Chest x-rays were read as normal in 60% of the evaluees. The range of abnormalities seen in the 40% who had abnormal findings are shown in Table 12 . The great majority of findings did not require any further work-up, but 12% who had a suggestion of an increase in left ventricular size would have required an echocardiogram if this were not part of the routine evaluation. In the 11 aviators with this finding, the echo was

Chest X-ray Findings	Number	Per Cent
Abnormal Pulmonary Vessel (old surgery)	1	1.06%
Degenerative Changes (including wedging of vertebrae)	9	9.57%
Density in lung or rib	3	3.19%
Compression Fracture	3	3.19%
Arteriosclerotic Changes	4	4.26%
Increased CT ratio, LVE, or left ventricular prominence	11	11.70%
Increased diameter of ascending aorta	5	5.32%
Old fracture (rib or clavicle)	3	3.19%
Old granulomatous disease	2	2.13%
Old histoplasmosis	1	1.06%
Scoliosis	2	2.13%
Surgical clips	1	1.06%
WNL	56	59.57%
TOTAL	**101**	**107.45%**

Table 12 Chest X-ray

normal in all but four. These four consisted of two cases of aortic insufficiency (one mild, the other moderate to severe) one case of "athletic heart" which resolved after an

exercise-free period, and one case of left ventricular wall thickness at the upper limits of normal (borderline LVH). Both of the aviators disqualified for LVH had normal chest x-rays. The number of abnormalities exceeds the total of 94 aviators because some had more than one finding.

Cardiovascular testing

Cardiovascular testing consisted of a resting ECG, an exercise treadmill test (ETT), a holter monitor, coronary artery fluoroscopy (CAF), an echocardiogram, and pulmonary function tests (PFTs). If either the CAF or the ETT was abnormal, then a thallium treadmill was done as well. The results of these tests will be considered individually and then collectively as they often resulted in the need for further testing including coronary angiography.

Electrocardiogram

EKG's were normal in the majority of the evaluees. Fourteen were found to have abnormal EKGs with 11 of these showing nonspecific ST or T wave changes. Five of these 11 also had abnormal treadmills with two undergoing coronary angiography. One had a normal cath; the other had SCAD. Other abnormalities seen included left axis deviation in two and one with minimal voltage criteria for LVH (found to have "athletic heart" on echo).Neither of the two aviators disqualified for LVH had this finding on ECG.

Exercise Treadmill Test

This was performed on all lisinopril evaluees according to the USAFSAM modified Balke protocol. Of the 94 initial tests, eleven (12%) were read as abnormal due to ST segment depression of 1mm or greater. Another seven had borderline results. Thirteen had some arrhythmia including PVCs, PACs, or paired beats (all ventricular). One person had six 3-beat runs of supraventricular tachycardia (SVT) and two had four-beat runs of ventricular tachycardia (V-Tach). The individual with recurrent nonsustained SVT was able to obtain a waiver for this condition, as did one of the individuals with V-Tach. The other individual also had MCAD and was disqualified for the combination of MCAD and V-Tach.

Of the eleven abnormal tests, eight resulted in coronary angiography (the other three were felt to be false positives due to age and analysis of risk factors). Five of these showed SCAD and resulted in disqualification. One had MCAD and the other one two had negative caths.

There were also ten aviators who had a hypertensive response with exercise treadmill testing.

Coronary Artery Fluoroscopy

This test was conducted if the aviator was 35 years or older. Seventy-nine aviators met this criteria, and of these, 18 (19.1%) were abnormal showing calcification in the distribution of the left anterior descending (LAD) coronary artery. Of these, 17 underwent angiography (one refused) and 10 of these had gradable coronary artery disease. Seven had SCAD discovered resulting in disqualification. The other three had

MCAD discovered resulting in a IIA waiver (one later progressed to SCAD on repeat cath). Seven had either normal angiography or had only intimal roughening noted. It is interesting to note that the four with intimal roughening had at least a portion of it in the proximal LAD roughly corresponding to the site of calcification.

Another four aviators had borderline fluoroscopy. Of these, only one had angiography performed due to a positive treadmill. He was found to have SCAD and was disqualified.

There were 57 negative fluoroscopies with 6 of these going to cath for other reasons. One had a positive cath with SCAD, the other five had negative caths. One other aviator had a negative fluoroscopy and a negative treadmill and thallium. He later developed angina. On a cardiac catheterization performed outside the ACS, he had a 90% occlusion of the mid-LAD. He had no disease noted in the proximal LAD.

Holter Monitor

All evaluees underwent holter monitoring and of these, 13 had a disqualifying abnormality found. These consisted of 9 with runs of SVT and one with V-Tach. There were also 2 with frequent PAC pairs and one with very frequent PVCs found. All of these aviators had further work-up and were given waivers for these abnormalities except the aviator with the 7 beat run of V-Tach, who was disqualified for severe aortic insufficiency. In no case did a finding on holter monitoring, by itself, lead to a disqualification.

Nearly all the aviators had a minimal number of PVCs, PACs or some combination of the two. These were considered normal or normal-variant holter monitors. Of these "normal" holter monitors, 41 aviators had only PACs, 35 had some combination of PACs and PVCs and 3 had only PVCs seen.

From these findings, there was no evidence that lisinopril caused the abnormal findings or that lisinopril is arrythmogenic.

Echocardiogram

Echocardiogram (echo) was done on all evaluees. Abnormalities were found in 30 (31.9%). These abnormalities can be subdivided into three categories: chamber enlargement or wall hypertrophy, signs of decreased left ventricular compliance, or valve disorders. The findings on echo are shown in Table 13. There were a total of 20 with wall or chamber enlargement; eight had left atrial enlargement (LAE), nine had either left ventricular hypertrophy (LVH) or left ventricular enlargement (LVE). Five had valvular disorders; two with mitral valve prolapse (MVP) and three with aortic insufficiency (AI). An additional five aviators had thickening of their aortic valve, a finding that was usually considered a normal variant. There were also two with an echo finding of decreased left ventricular compliance There were three with mild LVH. Two were disqualified and the other had athletic heart syndrome and the hypertrophy regressed after a few months of no exercise.

Echo Findings		
NORMAL	WNL	16
	NLVAR	48
ABNORMAL VALVE	AI	3
	AOV-Thickening	5
	MVP	2
	Dilated Aortic Root	1
CHAMBER OR WALL ENLARGEMENT- LEFT HEART	LAE, DEC LVCOMP	1
	LAE, E TO A	1
	LAE,LVH-BDL	2
	LAE-MILD	4
	LVH-BDL	2
	LVH-MILD	1
	LVH-MILD, LAE	1
	LVH-MILD, LAE, DEC LV COMP	1
	LVE- MILD	2
CHAMBER ENLARGEMENT RIGHT HEART	RAE	1
	RVE	2
DEC COMPLIANCE	E to A reversal	1
	Total	94

Table 13 Echocardiogram

In addition to these abnormalities, there were some findings that could relate to duration and severity of hypertension along with future potential for congestive heart failure. The finding of mitral E to A reversal suggests some stiffening of the left ventricle, which can be a forerunner of later diastolic dysfunction. An E to A ratio of less than 1 (indicating reversal) was found in 20 of the 94 evaluees (21.3%) and an additional 12 had a ratio of 1.0. Left atrial enlargement can also be a finding suggesting more long-standing hypertension and this was found in eight of these aviators. Strict attention to good control of the blood pressure to normal range is the best thing to do for these and reversal of these findings can occur with adequate treatment over time. It is important to screen certain hypertensive subgroups with an echocardiogram as noted by JNC VI[28].

Thallium Scintigraphy

This test was usually performed only on evaluees over the age of 35 who had either an abnormal ETT or CAF. In a few cases aviators younger than 35 had this test performed, especially if they had an abnormal ETT or CAF and there were other positive risk factors present. Of the 49 who had a thallium performed, there were 7 abnormal tests and 17 read as borderline. Six out of the seven abnormal tests underwent catheterization; the other was a 33-year old who was not catheterized. Two of the aviators with an abnormal thallium had normal treadmills and fluoroscopy. Both underwent catheterization and had no gradable coronary artery disease. Of the other 4 abnormal results, two had normal caths and two were abnormal with SCAD. Both of the aviators with SCAD had abnormal treadmills and abnormal fluoroscopy in addition to the abnormal thallium.

Pulmonary Function Tests

All evaluees had PFTs performed and of these 6 were abnormal. Five aviators had mild obstruction and one had moderate obstruction. None were symptomatic and there were no physical findings to suggest obstructive disease. None were current smokers nor did any have a history of smoking. None of these aviators had the "lisinopril cough". The age matched MVP group had a greater occurrence of both mild and moderate obstruction found on PFTs. This was not felt to be attributable to lisinopril and did not result in any disqualifications.

Cardiovascular Tests Taken Collectively

The ETT and the CAF were performed to screen for the presence of coronary artery disease (CAD). When one of these tests was abnormal, a thallium was done to complete the screening triad. Coronary artery catheterization was then performed to assess the presence of gradable coronary artery disease.

A total of 24 caths were performed in this group of 94 aviators. Two were performed outside the ACS after evaluation. There were also two other aviators with histories of caths performed prior to their entry in the lisinopril study for symptoms suggesting angina. Neither had gradable disease discovered. These were not counted in the 24 because they were performed for symptoms suggesting angina prior to these aviators taking lisinopril.

Of the aviators catheterized due to findings on their lisinopril evaluation, 13 were found to have gradable coronary artery disease (13.8%) leading to disqualification for 10 of these with the more significant lesions (SCAD). Only one of the three (discussed under disqualifications) with minimal disease was granted a IIA waiver and allowed to return to flying non-high performance aircraft.

Echo findings resulted in three disqualifications. Two of these were for LVH and the other was for moderate to severe aortic insufficiency.

PFT and holter findings by themselves did not result in any disqualifications or categorical waivers.

Centrifuge testing

Centrifuge testing was performed on aviators who flew high performance aircraft. There were a total of 22 aviators who underwent centrifuge testing. Table 14 shows a summary of the centrifuge runs. All aviators were felt to have adequate G tolerance based on their testing to return to high performance aircraft. Although there was a specific protocol for the centrifuge runs, due to the frequent occurrence of motion sickness, the medical monitor exercised some discretion in the actual number of runs performed and therefore there was some variance in the runs performed on this group. The means for each of the four main runs for the lisinopril group was compared to the means of a similar group of 435 aviators used as a control group for a previous study on MVP in aviators by Whinnery [54]. In all four groups the means for the lisinopril exceeded that of the control group and all were statistically significant differences when t-testing was done. In

looking at the pass/fail test done at the conclusion to determine G-tolerance with G-suit and strain, all passed this test, although not all achieved the standard of 7.5 G's for 15 seconds. Of the five who had less than 7.50, three were only tested at 7.00, and the other two were felt to have adequate G-tolerance based on their entire series. To reach a confidence level of 95% of finding a lowered G tolerance, we need to have at least 59

Case	GOR 1	ROR - Pass	GOR 2	GORS	Standard	Comments
1	4.00	2.80	3.90	6.70	8.00	No Arrhythmia
2	6.30	4.60	5.70	7.10	8.00	No Arrhythmia
3	3.60	3.10	3.60	5.40	9.00	2 PVC's
4	8.40	4.00		7.80	8.00	1 PVC
5	4.50	3.10	4.80	7.20	7.00	No Arrhythmia
6	6.40	4.00	5.50	6.20	8.00	1 PVC
7	6.06		5.54	7.50	7.00	No Arrhythmia
8	6.00				6.00	No Arrhythmia
9	5.60			7.40	6.60	No Arrhythmia
10	4.30	3.40	5.90	7.36	7.00	No Arrhythmia
11	4.70	3.70	4.72	5.49	7.50	No Arrhythmia
12	5.00	3.10	4.90	6.40	7.50	No Arrhythmia
13	6.54	5.01	7.27	7.03	7.50	PVC's, Bigeminy
14	4.75	3.50	5.50	8.10	7.50	5 PVC's, Bigeminy
15	4.50	3.50	5.50	8.70	8.00	No Arrhythmia
16	6.30			9.00	9.00	No Arrhythmia
17	5.80			9.00	9.06	No Arrhythmia
18	6.20			7.50	7.50	No Arrhythmia
19	5.00			6.50	9.00	No Arrhythmia
20	6.40			8.00	7.50	2 PVC's
21	5.50	3.60	5.00	7.50	7.50	No Arrhythmia
22	5.40	3.80	5.20	7.40	7.50	No Arrhythmia
Count	22	14	14	21	22	
Mean	5.51	3.66	5.22	7.30	7.71	
Std Dev	1.08	0.6052	0.8348	0.9824	0.7945	
Max	8.40	5.01	7.27	9.00	9.06	
Min	3.60	2.80	3.60	5.40	6.00	

Table 14 Summary of Centrifuge Testing

Lisinopril	GOR 1	ROR - Pass	GOR 2	GORS
Count	22	14	14	21
Mean	5.51	3.66	5.22	7.30
St. Dev.	1.08	0.61	0.88	0.98

Control Group	GOR 1	ROR - Pass	GOR 2	GORS
Count	434	434	434	434
Mean	4.65	3.34	4.45	5.56
St.Dev.	0.80	0.50	0.70	0.90

Lisinopril. vs. Control	GOR 1	ROR - Pass	GOR 2	GORS

T-Test	0.0000009	0.0415134	0.0003956	6.004E-17

Table 15 Centrifuge Means: Lisinopril vs. MVP

consecutive passes on testing, therefore, testing on the centrifuge will continue. Table 15 shows the t-test comparisons between the lisinopril group and the MVP control group.

Psychologic testing

Psychologic testing consisting of MMPI, MAB, and a brief interview with an aviation psychologist was performed on 83 of these aviators on their initial visit only. This was not part of the protocol, but was part of the Surgeon General's requirement for waiver. Of these 83, 79 (95%) had normal testing with one disqualified for depression and 3 having either incomplete or inconclusive results (due to English not being their first language). Out of the 79 normal evaluations, 15 were in the above average to very superior range of intellectual functioning on MAB testing (IQ tests).

MMPI testing combined with the interview did reveal a few potential aeromedical problems, not associated with lisinopril. Six aviators (7%) had alcohol concerns addressed and another 5 (6%) were counseled on concerns with stress in their life. In each case the primary flight surgeon on the case was aware of the problems and could have made a referral to psychologist in the absence of the requirement.

Testing showed that the means for the segments of the IQ testing were similar to those of the EFS group, although the age means were quite different. (Table 16) The lisinopril evaluees did not perform as well as the EFS group for the verbal IQ (VIQ), but the difference was not statistically nor clinically significant. The lisinopril group performed better than the EFS group in the performance IQ (PIQ) as well as the full scale IQ (FSIQ) and these differences were statistically different, though not clinically nor aeromedically significant. The MMPI scales were similar to those of an AFSOC control group with no differences approaching statistical nor clinical significance.(Table 17)

Lisinopril Study Group	Age	VIQ	PIQ	FSIQ
Mean	41.70	118.69	123.06	121.86
S.D.	5.90	7.41	9.92	8.20
N	94	84	84	84

EFS Student Data	Age	VIQ	PIQ	FSIQ
Mean	22.42	119.56	117.94	120.12
S.D.	2.35	6.82	8.58	6.84
N	1928	1931	1931	1931
Comparison by t-test of lisinopril means vs EFS means				
T-Test (p value)		0.2545546	0.0000001	0.0240323

Table 16 MAB (IQ Tests) Means: Lisinopril vs. EFS

Lisinopril Study Group	L	F	K	1	2	3	4	5	6	7	8	9	0	MAC
Mean	4.31	2.14	19.28	2.46	17.93	21.18	15.16	23.22	10.51	6.81	5.05	15.48	21.41	20.20
Std Dev	1.90	1.79	4.18	1.99	3.61	3.07	3.74	4.37	2.36	4.81	4.01	3.74	9.11	3.25
Count	85	85	85	85	85	85	85	85	85	85	85	85	85	85

AFSOC Pilots & Navigators	L	F	K	1	2	3	4	5	6	7	8	9	0	MAC
Mean	4.76	2.34	20.34	1.81	16.17	20.88	14.43	21.22	10.07	5.14	4.46	14.85	19.43	20.41
Std Dev	1.88	2.72	3.93	2.11	3.08	3.57	3.52	3.89	2.41	4.60	4.53	3.95	6.31	2.96
Count	145	145	145	145	145	145	145	145	145	145	145	145	145	145

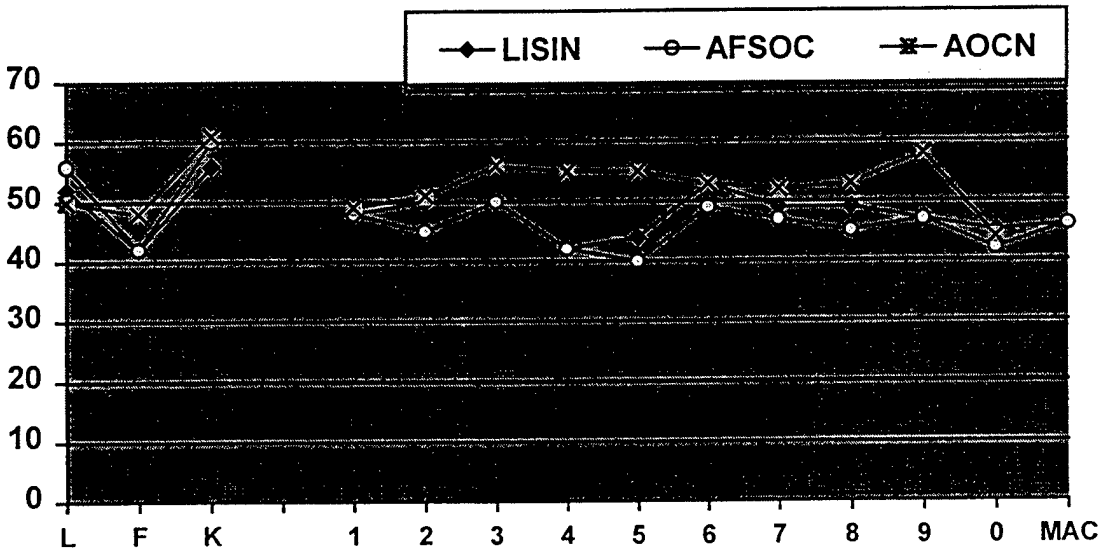
Lisinopril vs.AFSOC	L	F	K	1	2	3	4	5	6	7	8	9	0	MAC
T-Test (p value)	0.98	0.99	0.95	0.97	0.91	0.98	0.96	0.90	0.98	0.92	0.97	0.97	0.90	0.99

Table 17 MMPI Means: Lisinopril vs. AFSOC applicants

The MMPI scores were compared with an AFSOC selection group and with a group of aviators that were seen at the ACS and used to establish aviator norms.(Figure 1) Again, there were no significant differences across the scales.

Although the two tables and the figure appear to present compelling data to suggest that these aviators had no significant effect from lisinopril on neuropsychologic function, this is not the intention for presenting this data. While there appears to be no gross effects on intellectual function or personality for the whole group, differences would be detectable only with a study that utilized pre-testing without medication that is compared to a

Figure 1 MMPI Scales for Lisinopril, AFSOC Applicants and Aviator Norms



second series of tests after the aviator is on an established dose of lisinopril. Even then, these tests might not be sensitive enough to detect subtle effects on concentration and intellectual function.

Follow-up Evaluations at the ACS

A total of 36 aviators had at least one follow-up evaluation at the ACS. Twelve had 2 re-evaluations and four had three re-evaluations. Any changes seen on retesting were discussed under each individual test section. Five aviators needed an increase in the dosage to maintain control of the blood pressure; two aviators had a decrease in dosage over time. Overall, retesting at the ACS had few significant findings with a few notable exceptions including the one aviator who was disqualified when his blood pressure failed to be controlled on a maximum dose of lisinopril. In December 1996, retesting at the ACS was discontinued in favor of local re-evaluations.

DISCUSSION AND LITERATURE REVIEW

Hickman describes eight components of an ideal medication for aviators with hypertension[21]. The blood pressure should be controlled as measured on a five-day blood pressure average, and the medication should not affect cognitive or motor performance during acceleration, heat, altitude, task saturation, and time zone changes. The medication should not have any side effects that lead to sudden incapacitation, but any defined side effects should be rare, predictable, and treatable; side effects need to be discovered before the flyer is waived. The medication should not hide symptoms or signs of other diseases (i.e., beta-blockers hide cardiac ischemia). The medication should be long acting and low cost; there should be years of clinical experience with the medication in other aviators; and lastly, it should not require expensive or dangerous tests to detect side effects or performance decrements. It was noted that thiazide diuretics met all of these requirements and that the ACE inhibitors met only the first six criteria. The problems of lisinopril include no long-term experience and the cost. At this point in time there has been more experience with lisinopril, especially with the results of this study group, and there is less issue with the cost compared to other available agents.

LISINOPRIL

Lisinopril is a long-acting form of a class of drugs known as the ACE inhibitors with ACE standing for angiotensin converting enzyme. The mode of action for lisinopril, like the other ACE inhibitors, is the suppression of the renin angiotensin aldosterone system. The exact effect is to block angiotensin converting enzyme, which converts angiotensin I to angiotensin II. This blockage leads to an increase in angiotensin I and a depletion of angiotensin II. This leads to a decrease in vasopressure activity and to a decrease in aldosterone secretion, two of the effects of diminished levels of angiotensin II. The vasoactive effects result in mild vasodilation and a decrease in the total peripheral resistance[35,45]. The overall effect is to lower blood pressure. The serum half-life of lisinopril is about 12 hours with peak serum concentrations attained after about seven hours. This permits its use as a once-a-day medication. Dosage ranges form 2.5 to 80 mg per day although some authorities recommend limiting it to 40 mg per day[35,56]. It is excreted unchanged by the kidneys without metabolism in the liver[35].

Lisinopril received FDA approval for the treatment of hypertension in 1987[35].
It has been widely used for that indication since that time with many double-blinded controlled studies attesting to both its safety and its efficacy[7,9,15,20,]. The side effects that had been reported on lisinopril include greater than placebo effects of dizziness, headache, upper respiratory symptoms, hypotension, and cough[45]. Cough is more of an aggravation, but is the most common side effect with lisinopril, occurring in 5-20% of those treated[26]. Angioedema of the face and neck is probably the most severe reported problem, but fortunately is quite rare. A case series on five cases by Jain had four patients with this side effect on the ACE inhibitor lalorpril, and one in a patient on lisinopril. The risk factors for this side effect include obesity, previous head and neck surgery or a history of intubation[27]. Deterioration of renal function has also been reported in certain clinical states such as volume depletion and severe bilateral renal artery stenosis[41]. However, ace inhibitors have been shown to provide protection against the progression of renal insufficiency in a variety of other renal diseases[38]. In fact, JNC VI recommends that patients with hypertension and renal insufficiency should receive an ace inhibitor preferentially over other agents unless specifically contraindicated[28]. Lisinopril does have a "boxed warning" in the PDR, which concerns its usage in pregnancy. ACE inhibitors can cause injury and even death to a developing fetus if administered during the second and third trimester. Therefore ACE inhibitors are contraindicated in pregnancy[45].

Another measure of the tolerability of the drug would be its effect on the quality of life. Lisinopril has been looked at in this regard in a study by Frimodt-Moeller using general health questionnaires. They noted that the quality of life after discontinuing a thiazide diuretic and starting lisinopril was significantly improved[16]. In a study by Croog, et al which compared quality of life with questionnaires among three drugs (captopril, propanolol and methyldopa with or without HCTZ), captopril had the highest score[11]. Another beneficial effect of the ace inhibitors is their lack of effect on lipids, an effect that doesn't change over two to three years of therapy. They have also been shown to decrease insulin levels and increase insulin sensitivity[34].

The ACE inhibitors are attractive for use in aviation because they do not affect the sympathetic nervous system in a direct fashion as the alpha and beta-blockers. Although they are considered vasodilators, they do not induce a reflex increase in the heart rate[57].

As a class of drugs, ACE inhibitors have found to decrease systemic vascular resistance, decrease blood pressure, and improve cardiac functioning[29]. ACE inhibitor therapy has also been shown to decrease left ventricular hypertrophy[17]. In a comparison trial, lisinopril has been proven more effective as a step 1 drug than hydrochlorothiazide in a 52-week study[31].

HYPERTENSION

Hypertension has been widely defined as blood pressure that exceeds a systolic of 140 mmHg and/or a diastolic that exceeds 90 mmHg. Over the years, there has been much controversy concerning at what level hypertension should be treated and the best way of

determining that a person is, in deed, hypertensive. It is not unusual for persons to have periodically elevated pressures, especially on the visit to their physician's office. This led to a description of one form of hypertension as "labile" hypertension, which, for the most part, was not treated, but was followed with blood pressures averaged over five days. "White coat" hypertension is a similar category of mild hypertension that provokes much controversy. JNC VI describes this form of hypertension and suggests the use of home blood pressure monitoring as well as 24-hour ambulatory blood pressure monitoring to better define this subset of suspected hypertensives[28].

Accurate, consistent techniques for the measurement of blood pressure with a cuff sphygmomanometer is also important. There is a method for measuring the blood pressure that has been described in the hypertension practice guidelines and in a separate position paper by the American Society of Hypertension[2].

The prevalence of hypertension in the United States overall as reported in NHANES III, is about 24% or about 43 million people. The subset of this population that most closely approximates the demographics of this study group is the non-hispanic white male population. According to NHANES III this population has a prevalence of about 25.6 %. Breaking this group down by age reveals a prevalence of about 15% among the 30-39 age group and about 22% among the 40-49 year old age group[6].

The prevalence of hypertension in USAF aviators is about 1%; the prevalence of hypertension in FAA pilots is about 3%[5]. There is an obvious difference in the prevalence, which may be due to the healthy group of persons who enter flying training as a rule, or it may be that flight surgeons are under identifying aviators with hypertension. The reasons that this group might be under identified are the negative consequences potentially present with being identified as a hypertensive and being placed on medication. Aviators, as a rule, do not wish to carry a waiver for any diagnosis and especially do wish to be treated with long-term medication. The fact that the diagnosis of hypertension is based on an average of ten different, somewhat subjective blood pressure readings is also an added incentive to delaying this diagnosis

In regard to what the other services do with hypertension, both the Navy and the Army have a more liberal policy when it comes to medications in the treatment of hypertension in their aviators. According to the waiver guide for the Navy, treatment for hypertension is initiated with lifestyle modification and hypertension controlled by diet and exercise alone does not require a waiver. The use of ACE inhibitors, including captopril, enalapril, lisinopril, or quinapril, is encouraged as first-line therapy. They do not approve beta-blockers for flying. Hydrochlorothiazide is approved, as well; however, drugs combining triamterene and hydrochlorothiazide are not approved for waiver. This includes Dyazide® and Maxzide®. Other drugs not approved for treatment include Lopressor®, Minipress®, and Procardia®. The ACE inhibitors are approved for both non-high-performance and high-performance flight.

The Army probably has the most liberal policy for the use of medications for hypertension in aviators. Their treatments include ACE inhibitors and alpha blockers,

including prazosin, doxepin, and terazosin. Beta-blockers can be used in air traffic control personnel only. These include atenolol, metoprolol and propanolol. Calcium channel blockers also are limited to air traffic control (ATC) personnel as is clonidine. Diuretics, specifically the lose-dose thiazides, preferably potassium sparing, and those in combination form can be waivered. Loop diuretics are not approved for flying classes.

As for other military services, there is some information available on what the United Kingdom uses in the treatment of hypertension in aviators. The British have approved for use in aircrew calcium channel blockers, angiotensin converting enzyme inhibitors, and diuretics. The policy for angiotensin converting enzyme inhibitors is that pilots can fly with on it, but not in solo flight. They must have a copilot qualified for that type of aircraft, as does the navigator. The air engineer can return to unrestricted flying[4].

The medications used for aviators must lack any effect on G tolerance. There are two studies that attempted to demonstrate the effect of anti-hypertensive medication on G tolerance. One of these was written about captopril[43] and the other was written about hydrochlorothiazide[44]. The HCTZ study was reported in 1972 and tested 6 non-hypertensive individuals in the centrifuge before and after receiving HCTZ. The dosage was 50 mg of HCTZ twice a day. Although a common dosage at that time, this dose would be considered excessive today. These individuals were tested at two and four weeks after starting the medication. The authors reported statistically significant decreases in mean G tolerance for this group at the two-week and four-week points. The study with captopril used 7 normotensive volunteers and only treated them for 4 days. The investigators noted a statistically significant decrease in the G tolerance with captopril. Although there were no statistically significant differences in blood pressure after being placed on the captopril, the authors felt that the medication was responsible for the reduction in G tolerance. They concluded that the hemodynamic effects of the ACE inhibitors would be similar in hypertensive patients and would have a similar deleterious effect on Gz tolerance. Often the peak orthostatic effects of anti-hypertensives are noted during the first week of treatment[45] so these volunteers were being tested at the time of the greatest likelihood for showing an orthostatic effect.

Both of the studies showed decrease in G tolerance with the anti-hypertensive medications given to normotensives. Both studies concluded that testing done with hypertensive individuals should follow. Neither drug changed the resting blood pressures of these normal volunteers to a statistically significant degree. It was assumed that these effects would be seen in a hypertensive individual who is taking the medication to lower the blood pressure to the normotensive range. However, it is believed that hypertension itself will increase G tolerance[21,52]. Whether or not a treated hypertensive with normal pressures noted on five-day blood pressure averages would continue to have a normotensive response to increased +Gz despite the medication is unknown.

HYPERTENSION AS A RISK FACTOR

Hypertension is a known risk factor for both coronary artery disease and atherosclerotic vascular disease. Multiple studies, including the Framingham studies, MRFIT, SHEP trial and others, have demonstrated that treatment of hypertension leads to a decrease in

the morbidity and mortality from coronary artery disease and stroke[1,18,43,47,50,51]. There have been other trials focusing primarily on a more elderly population[3,13,47]. McMahon et al did a review of randomized control trials, seeking to show the effect of drug treatment for hypertension on morbidity and mortality from cardiovascular disease. The data for this paper were summarized from about 250,000 patient years of study and included more that 2,300 deaths and 1,300 nonfatal strokes and myocardial infarctions. In looking at the trials with predominantly mild to moderate hypertension, there was seen a reduction in all cause mortality and stroke incidents among subjects receiving treatment. The pooled data showed an 11% reduction in total mortality. The conclusion of this article was that, although a decrease in death and morbidity from stroke is readily apparent in these studies, it is more difficult to show an effect of treatment on morbidity and mortality of coronary heart disease[37]. The figures for reduction of stroke death are impressive and the numbers for coronary artery disease are less so, but still are significant. Herbert et al[19] points out that while the percent reduction in CHD deaths is less than that of stroke (16% for CHD compared to 40% for stroke in their series), the absolute number of deaths prevented is similar due to the greater prevalence of CHD. It has also been shown in recent studies that the level of the blood pressure is directly related to risk of mortality and morbidity and, therefore, that even mild degrees of hypertension when treated will result in a lowering of overall risk.

Collins, et al reviewed the results of 14 unconfounded trials of anti-hypertensive drugs used to treat hypertension and showed a 42% decrease in stroke and a 14% reduction in CHD[10]. An extensive review of available studies by Stamler, et al.[48] on blood pressure and cardiovascular risks presents compelling evidence that both systolic and diastolic blood pressure have continuous, graded, independent relationships to incidence and mortality from coronary artery disease and stroke. In addition they found a similar strong relationship to cardiac abnormalities including those on chest X-ray, ECG and echocardiogram. All-cause mortality and life expectancy were also outcome variables strongly affected by the blood pressure. These findings support a recommendation that treatment of patients with mild hypertension should be considered early, before damage to end organs occurs. The above studies reveal that there may be some consequence to not treating mild hypertension. They also strongly support the fact that hypertension is a modifiable risk factor for coronary artery disease. It has been shown that a 5 mm Hg reduction in diastolic blood pressure decreases the risk of stroke by a third and coronary artery disease by a fifth[10].

CURRENT USAF APPROACH TO TREATMENT OF HYPERTENSION

The U.S. Air Force approach to the diagnosis of hypertension involves a strategy similar to that outlined in the JNC VI[28]. The current approach to hypertension in USAF aviators, taken from AFI 48-132 is included as attachment 3. If an aviator presents to the flight surgeon's office and has an elevated blood pressure, he undergoes a five-day blood pressure check consisting of 10 blood pressures measured over a five-day period. These are averaged and, if this average exceeds 140 mmHg systolic or is 90 mmHg or more for the diastolic, the aviator is diagnosed as having mild hypertension. They are given a six-month trial with nonpharmacological treatment, generally consisting of exercise and a

low-sodium diet. After the six-month period has ended, a second five-day blood pressure average is done and, if this again exceeds the 140/90 mmHg mark, they are started on treatment. If the blood pressure average does not exceed that mark, they are followed annually with blood pressures measured during physical examination. If, however, on the five-day blood pressure, their average exceeds 160/100 mmHg, they are immediately begun on pharmacologic treatment without a period of nonpharmacological treatment. If they are treated with medication, there are two choices available to the flight surgeon at this time. One is the thiazide diuretics and the other is lisinopril. There is a dichotomy in the amount of effort that must go into treating with either drug. If the aviator is treated with thiazide diuretics, all that is required is that he has a complete history and physical examination, a series of blood tests, and an ECG. He must take the drug for 30 days, and he is grounded during this 30-day period. At the end of the 30-day period, a five-day blood pressure is done and, if the average is below 140/90 mmHg, a waiver is applied for and, once granted, the aviator can resume flying duties. The waiver allows the aviator to be tracked because he cannot resume flying status until the waiver is renewed each three years. On the other hand, if it is found that the aviator would do better on lisinopril or if he fails treatment with thiazide diuretic or if he has a side effect with the thiazide diuretic, he is begun on lisinopril. Again, there is a 30-day period to monitor for early side effects, and the work-up does consist of a history and physical examination with lab work and an ECG. If at the end of the 30 days a five-day blood pressure average is normal, the aviator comes to the Consultation Service at Brooks Air Force Base. Here, he is entered into the lisinopril protocol and a series of tests are done, which were described earlier in this paper. The point is that a central evaluation is much more arduous for the aviator, and it is not inconceivable that this might influence the choice of medication.

RECOMMENDATIONS

The recommendations presented are derived from the results of the study and from a review of the current literature on hypertension. The work-up for hypertension continues to be based on the current recommendations of JNC VI modified somewhat by the needs of this population.

The first indication that an aviator might be hypertensive is an elevated blood pressure during a routine office or dental visit. Traditionally this has triggered the time honored five-day BP check. If the average of five days of office blood pressures is 140 or greater for the systolic pressure, or 90 or greater for the diastolic pressure, but is less than 160/100, the aviator is placed on a six-month program of diet and exercise (waiver guide algorithm). No changes in this general approach are suggested at this time, but eventually we need to consider the findings of JNC VI, which suggests that diet and exercise should be initiated for the "high normal" group of blood pressures (130-139/85-89)[28].

The general prevalence of hypertension in USAF aviators is difficult to calculate. If one takes the Military Personnel Center (MPC) figure of total aviators as the population at risk, and uses the total number of aviators in the waiver file with waivers for high blood pressure treated with medication as the numerator, the prevalence is about 1%. We

currently have no means for assessing how many aviators each year are diagnosed with "borderline" or "minimal" hypertension who are on the six-month diet and exercise treatment routine. One way to determine this number would be to require a local waiver for those being treated with the six-month program of diet and exercise. This would help define the number of borderline hypertensives who might progress to hypertension. This algorithm proceeds with this and requires those who qualify for non-pharmacologic treatment of hypertension be tracked with a local waiver package approved by the local 48A3. The packages should be sent to MAJCOM for tracking. Each of the MAJCOMs could then generate statistics on the prevalence of borderline hypertension and send information to be the Aeromedical Consultation Service (ACS) via regular updates to the waiver file for collection across the Air Force.

Many have questioned the reliability of the five-day blood pressure. The major point of controversy is if we're finding "white coat" hypertension with this method that does not require treatment. Many physicians complement their office blood pressures with home blood pressure monitoring by the patient using one of the many commercially available home blood pressure units. The problem with this approach is that the large studies from which we derived our current treatment approaches to hypertension were derived from office based blood pressure measurements. The effect on morbidity of hypertension treatment is based upon these studies. If the physician decides not to treat a patient with elevated office blood pressures based on normal values achieved in the home, is he failing to prevent future morbidity due to hypertension?

At this time the algorithm suggest that the treating physician can supplement the office pressures with home blood pressure readings to help him to arrive at a decision for or against a six-month non-pharmacologic treatment. The physician should keep the above caveat in mind. This decision should be based upon the physician's own clinical opinion that the aviator does or does not have clinical hypertension.

If, during the five-day blood pressure check, an average is obtained which is greater than or equal to 160/100, then pharmacologic treatment needs to begin and the second stage of the algorithm should be started.

Non-pharmacologic treatment

When aviators' five-day blood pressure average is greater than or equal to 140/90 but less than 160/100, the flight surgeon should begin non-pharmacologic treatment including diet to achieve ideal body weight and exercise to achieve aerobic conditioning. There are multiple studies showing that weight loss of even 10 pounds can reduce high blood pressure[5]. Achieving and maintaining good aerobic conditioning also has been shown to reduce blood pressure[5]. The selection of a diet should also consider the aviator's current lipid status. Although lipid studies are not part of this non-pharmacologic section, they can be obtained at this time. With the initiation of preventive health assessment (PHA), there should be lipid studies on the medical record as part of an overall coronary artery disease risk factor program. If elevated lipids need to be addressed with diet, the flight surgeon can do this in conjunction with the non-pharmacologic treatment of elevated

blood pressure. The 24 Mar 97 memorandum on the Coronary Primary Prevention Program by Pickard is included as attachment 4 and it can be used to address the risk factor of elevated lipids. The DASH diet was included in the JNC VI as a sample diet for hypertensives .and it can be used as a diet treatment for hypertension.[28]

The follow-up of hypertension treated with diet and exercise has not been specifically addressed in the previous algorithm. Unfortunately some aviators are lost to follow-up. The flight surgeon should strive to make the aviator accountable for a good effort on this six-month program by following the aviator at monthly intervals (as a minimum) and tracking progress for both the blood pressure and the weight. The resting pulse rate can be monitored for response to an aerobic exercise program. At the end of six months, another five-day blood pressure should be accomplished. If the aviator was successful in reducing his blood pressure below 140 over 90 on the five-day average, than the 48A3 can recommend continuing the waiver. This information should be sent to both MAJCOM and to the ACS.

JNC VI has also addressed the issue of 24-hour ambulatory monitoring of blood pressure[28]. There's still a great deal of controversy on how to incorporate this modality into an approach to the diagnosis of hypertension. There is also the problem of cost and availability of this modality as well as standardization of a blood pressure that would signify hypertension that requires treatment. Therefore, if ambulatory monitoring is available, the information obtained from this would be welcome additional data, but clinical decisions cannot at this time be based on this modality.

Another controversial issue is the level at which borderline hypertension should be diagnosed. JNC VI suggests that 130/85 may be a more appropriate level to initiate non-pharmacologic treatment. Advising aviators to begin a program of diet and exercise at this level of blood pressure on an informal basis is at the discretion of the local flight surgeon, but it is highly encouraged based on the evidence from JNC VI.

Pharmacologic treatment of hypertension

Once the six-month trial has been completed, and a second five-day blood pressure average has been found to equal or exceed 140/90, the aviator is then diagnosed with hypertension. At this point the flight surgeon should make a decision on initial treatment and perform the work-up necessary to begin treatment.

The first step is to classify the hypertension as either primary or secondary hypertension. Secondary hypertension is not common (various studies quote 1 to 5 per cent), but it can occur and it was seen in the lisinopril study population. Entry criteria did not allow evaluation of secondary hypertension as part of the lisinopril study group, however there were four aviators with hypertension secondary to renal disease evaluated separately. The initial work-up should help to classify the aviator as either primary or secondary hypertension. Exotic testing is not necessary in the majority of cases and without historical or clinical lab evidence to suggest a secondary diagnosis, there is little justification for pursuing a diagnosis. Some authorities suggest a renal ultrasound to

include the adrenals as part of the work-up[22]. The Aeromedical Summary should make note of how the diagnosis of secondary hypertension was excluded.

The flight surgeon should perform a good history and physical. It should address factors such as those listed in table 18 as a minimum. In general, it should focus on when and under what circumstances the hypertension was initially detected, previous treatments (including non-pharmacologic), and any other contributing conditions. The past medical history should note any other significant history, other medications, other waivers, and any allergies to medications. The family history should focus on diseases in first-degree relatives, especially hypertension, which when present supports the diagnosis of essential hypertension. A family history of coronary artery disease in a first-degree relative should also be noted in a first-degree male relative <55 years of age or a female <65 years of age. A family history of renal disease may indicate an increased suspicion for secondary hypertension. The review of systems should focus on any other symptoms that the aviator has, especially those that may denote secondary organ damage from the hypertension.

HISTORY AND PHYSICAL
History
HBP history (review chart)
Previous treatment and results
Other significant past conditions
Other medications
Other waivers
Allergies
Risk Factors for CAD
Family history (HBP, CAD, renal, DM)
ROS
Physical Exam
Vital signs(BP both arms, ? leg, pulse)
Fundus
Neck bruits and thyromegaly
Lungs
Heart (PMI, murmur, S4)
Abdomen (bruits, masses)
Extremities(pulses, bruits)
Neurologic (tremor)

Table 18 History and Physical

The initial laboratory work-up should be geared toward detecting secondary hypertension, for detecting end-organ damage, and for establishing a baseline to detect any side effects of the chosen medication. This work-up can be different depending on the medication selected, but to simplify matters, the same general approach is used for both categories of medication. The initial laboratory tests are shown in table 19.

INITIAL LAB
CBC
Electrolytes
Liver Function Tests
Urinalysis
BUN, creatinine
FBS
Lipid Panel
Calcium, Uric Acid

Table 19 Initial Lab

A complete blood count (CBC) is used to check the white cell count (WBC), hemoglobin, and hematocrit. The chemistry panel and liver function tests are used to check electrolytes and liver test baseline values. These tests can be affected by anti-hypertensive medication. The BUN and creatinine, in addition to checking kidney function, and also provide a baseline since these tests can be affected by both lisinopril and thiazide diuretics. The urinalysis primarily looks to confirm the absence of protein and glucose in the urine. Additional baseline tests, especially for the diuretics, include serum calcium and a serum uric acid. Lipid studies, including the cholesterol, the HDL, the LDL, and triglycerides should also be done not only to establish baseline values, but also to use for later coronary artery disease risk factor determination. The EKG and the chest x-ray should also be obtained at this point both as baseline tests and for detection of the secondary effects of hypertension.

The issue of whether or not to include an echocardiogram as part of the initial work-up for pharmacologically treated hypertension is controversial. JNC VI suggests that in certain subgroups an echocardiogram should be considered in the initial work-up[28]. Aviators can be considered a subgroup that should receive this test because of their unique occupational requirements. This is not unprecedented. Currently all aviators get an echocardiogram as part of their screen for entry into pilot training. This is done to detect disorders that are not conducive to a long-term career in aviation. In this subgroup of aviators, detection of left ventricular hypertrophy is important and should be done as part of the initial work-up. Lisinopril study data supports the use of echocardiography in hypertensive aviators. The yield of frankly abnormal and borderline findings, as well as the three disqualifications based on echo findings, makes it difficult to avoid this test in this population. There were 30 aviators (32%) with a finding on the echo, with 20 of these having chamber enlargement or wall hypertrophy. There was also 20 identified with mitral E to A reversal, which can be an indicator of early diastolic dysfunction. The reversal indicates that the normal flow velocities measured on echo across the mitral valve into the left ventricle have been altered due to reduced compliance of the left ventricular wall during diastole. This information could be of assistance to the treating physician for decisions on how aggressive to be in treating the aviator with hypertension. As stated by Hull in his article on arterial hypertension in aviators "...diastolic dysfunction may precede definite LVH, and is probably one of the earliest markers of hypertensive target-organ damage and an indication for active anti-hypertensive measures"[22].

Selection of initial medication should be based on an assessment of the individual patient. Both diuretics and lisinopril are effective in the treatment of hypertension. Lisinopril is thought to be more effective in white populations and diuretics are thought to be more effective in black populations[28]. Diuretics also have the added bonus of having long-term studies that show them to be effective in the prevention of coronary heart disease (CHD) mortality and morbidity. Although studies are pending with lisinopril and other hypertensive agents, only the diuretics and beta-blockers have been shown to prevent CHD mortality. Diuretics have the disadvantage of causing hypokalemia in many patients. They also can affect lipids and uric acid. A recent study showed that these effects on the lipids persist in follow-up over 2-3 years[34]. Once a medication has been selected, potential side effects should be explained and looked for, once the patient is on a stable dose of the medication. The initial trial of medication is for 30 days. Aviators treated with either medicine need to be grounded during the initial 30 days and cannot be returned to flying status until a waiver is approved.

The rest of this discussion will center on the use of lisinopril as the chosen medication. Three days to one week after starting lisinopril, a BUN and creatinine should be checked since they can rise quickly in a patient with renovascular hypertension. If the creatinine has arisen by 1 mg over the baseline value, lisinopril should be discontinued and a work-up for renovascular hypertension initiated. This recommendation is also part of the proposed hypertension practice guidelines for the USAF.

During the initial time the aviator is on lisinopril, they should be encouraged to report any side effects, including dry cough, orthostatic symptoms, headache, nausea, dizziness or difficulties with concentration. After 30 days, a five-day blood pressure should be performed along with repeat lab values and an EKG. An Aeromedical Summary (AMS) should be generated which covers all the above findings. This should be sent to the MAJCOM with an information copy sent to the ACS. All EKG and echocardiograms should be sent to the ACS as well. The Aeromedical summary should include the basic information listed in attachment 6 but should also address the items in table 20.

A review of coronary artery disease risk factors should be done during the initial work-up. Special attention should be directed to those aviators 40 years and over undergoing this initial work-up for medications. If they are 40 or over, a coronary artery disease work-up should be done as part of the waiver package. This work-up should include exercise treadmill testing (ETT) and coronary artery fluoroscopy (CAF). If either of these tests are positive, the aviator must be referred to the ACS for the work-up for potential coronary artery disease. It is best to perform the ETT once the blood pressure is controlled near the end of the 30-day trial of medication. The ETT should be done according to the USAFSAM modified Balke protocol (see attachment 5). Fluoroscopy can be done as described in the reference by Loecker[52]

The use of the combination of the ETT and the CAF was determined to be the best combination for detecting gradable coronary artery disease in the lisinopril study group

AEROMEDICAL SUMMARY INITIAL EVALUATION
History of hypertension, how long present, previous 5 day results, previous treatment including non-pharmacologic with results and duration of treatment.
If applicable, reason for discontinuing previous treatment
List any side effects or the absence of side effects.
Work-up for secondary hypertension, if applicable
Dosage used to control BP and 5 day BP average.
Risk Factors for CAD
Any additional conditions or waivers
Any additional medications
Physical exam findings
All lab results
ECG, CXR and echo results
Results of screening for CAD, if applicable

Table 20 What to include in the AMS

population. Positive predictive value in a population with a low prevalence of CAD is low. This hypertensive population has a higher prevalence of CAD and when stratified by age and the presence of an additional risk factor, its prevalence increases. If only those that are male and 40 or older, or female and 50 or older are selected, there are 61 aviators to consider. Using this as the at-risk population, the rate of positive ETT or CAF is 21/61 or 34.4 % and there is only one 39 year old aviator with SCAD missed .By selecting those with one additional risk factor, the group is reduced to 37. If one uses this group of 37 as the population at-risk, the rate for either a positive ETT or a positive CAF is 15/37 or 40.5%. However this is at the expense of missing five aviators who lacked positive risk factors and would not have been screened (all 5 had SCAD). One of these five was the individual who went on to develop angina after being disqualified for SCAD. Although there is a gain in the rate for positive tests, and the number screened is substantially less, missing aviators with SCAD misses the point for the screening. Rates for sensitivity and specificity for various testing strategies is shown in figure 2.

In each case, high levels of sensitivity are usually achieved at the expense of specificity. The goal is to try to achieve the lowest possible number for false negative, the bottom left box of the 2x2 tables. That is achieved with the boxed 2x2 table which represents the current recommendation.

If either the exercise treadmill test or the fluoroscopy is positive, the aviator will need be sent to the ACS for continued work-up including a thallium scan. A decision on cardiac catheterization will be based on the MACADE risk. The MACADE formula is thoroughly explained in attachment 7. It uses the risk factors and the results of the three screening tests to derive a number that aids the decision on catheterization.

Lisinopril

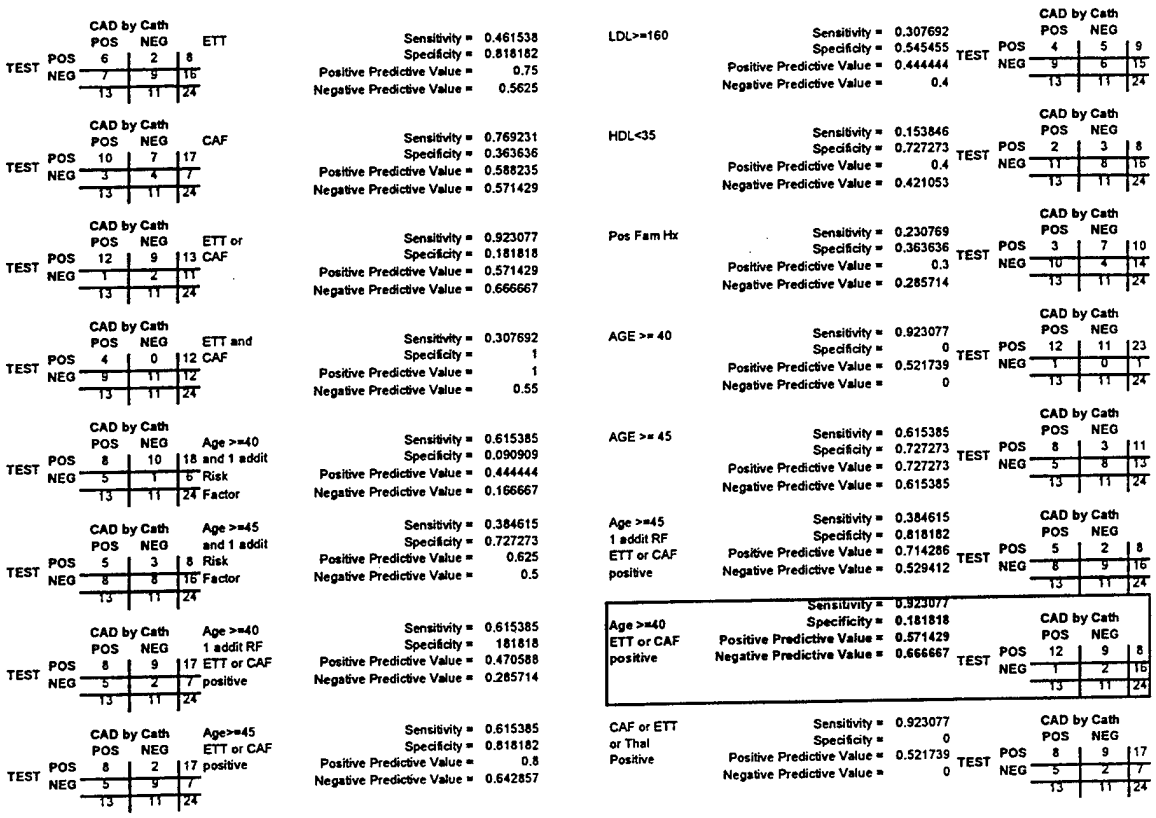


Figure 2 Sensitivity and Specificity of Various Testing Strategies

For aviators flying high-performance aircraft who are treated with thiazide diuretics, enough experience been gained over 25 years to allow them to return to the cockpit without centrifuge testing. There is one study that suggested that non-hypertensive volunteers placed on thiazide diuretics had decreased G tolerance[29]. For those placed on lisinopril there is only the experience of the 22 aviators who been evaluated with centrifuge testing at the ACS. The data shows that this group did quite well, however this is insufficient to make a general statement that lisinopril will have no effect on G tolerance. As a matter fact, there is anecdotal evidence to suggest diminished G tolerance from one aviator on Lisinopril. There's also a single study that suggests that captopril (another ACE inhibitor) decreases G tolerance in non-hypertensive subjects placed on it[8]. The two weaknesses of this study are that it deals with non-hypertensives, and that the time of treatment was very short (4 days). Although the data from the lisinopril study suggests no significant effect on G tolerance, until there is better statistical support for this fact, there will be a need to continue to test high-performance aviators in the centrifuge. A total of 59 aviators need to be tested for a statistical significance of 5 percent. This is a crude measure, but does give a better indication that the performance in the centrifuge of these aviators is not due to chance alone. There is also fact that in the aircraft, the aviator not only has the G straining maneuver, but also often has protective equipment including the G suit and Combat Edge, depending on the aircraft. All of these would supplement the native G tolerance. Native G tolerances measured by the GOR has been comparable to previous groups most notably the control group for a MVP Study.

Because all high-performance aviators now undergo centrifuge testing at Holloman Air Force Base, which includes GOR and GORS, the results of these tests can be available for comparison in future G tolerance testing and should be noted in the Aeromedical Summary. Significant decreases in native G tolerance that cannot be overcome with a proper G Strain should be referred for retraining in accordance with AFI 11-404. (attachment 7)

A modified centrifuge protocol is proposed which will collect similar data, but will hopefully produce less vertigo and nausea. This new protocol is included as attachment 8. It eliminates some of the redundant centrifuge runs while preserving those that provide the most information on the cardiovascular responses to +Gz. In order to provide enough time under +Gz to evaluate the incidence of arrhythmias, the training runs should all be performed. The GOR2 is eliminated. Although it was felt that this second GOR would eliminate the anxiety- driven increase in the GOR1, nearly half of the lisinopril evaluees actually performed better on the GOR 2. The other runs to be eliminated are the ROR runs. According to Whinnery[55], this series of runs tests the neurologic component of G tolerance. According to Paul[43], ace inhibitors do not affect this component and that fact was born out by his data. This appears to be confirmed by the data from the lisinopril group as well in that their ROR tolerance was not reduced compared to the control group. Another problem with the ROR runs was that there was a difference in the onset speed of the centrifuge between the control group and the lisinopril group. The control group did their ROR runs at 1G/sec and the lisinopril group was at 6 G/sec. It is thought that the increases in speed may have been a factor in the problem with motion sickness. Therefore there seems to be no justification for keeping the ROR runs.

How often to re-evaluate hypertensive aviators is another concern. Aviators taking thiazide diuretics for hypertension are re-evaluated annually. Annual re-evaluation should be adequate for aviators taking lisinopril once they are on a stable dose and show no evidence of side effects. Re-evaluation for changes in dosage of lisinopril should be done and should include laboratory tests and five-day blood pressure checks. How often to perform re-testing of echocardiography and coronary artery disease screening should be based on how well the aviator is controlled on medications and whether or not other controllable risk factors for CAD have been addressed. As a minimum, treadmill testing for this at-risk group should be done every three to five years if the test is initially negative. If positive, then re-testing should be done according to established policies for a positive treadmill. Coronary artery fluoroscopy should also be done every 3-5 years except for those aviators with a positive result on initial testing, who should not be re-tested. With advancing age, risk increases, so this policy should not be viewed as inordinate. Echocardiography should be done every five years after the initial baseline (if normal) once the aviator reaches age 40 Abnormal echocardiograms should be repeated with a frequency dictated by the nature of the abnormality.

Repeat centrifuge testing is not part of this algorithm, but certainly is available. If the treating flight surgeon has clinical concerns that there have been changes over time suggesting a decrease in G tolerance (orthostatic symptoms, complaints by the aviator of decreased G tolerance, or problems noted on G tape reviews), then re-testing in the

centrifuge may be indicated. Policy requiring centrifuge re-testing each time the dosage of lisinopril is changed is not recommended, since this would be a logistic nightmare and would interfere with the smooth functioning of the aviator and his squadron.

Annual re-evaluation should include a good history and physical exam including an interval history, laboratory testing, ECG, and five-day blood pressure. These findings can be documented as part of the PHA. The results of the annual re-evaluation should be documented on a brief aeromedical summary and a copy of this should be sent to the ACS for follow-up of the data for this group. MAJCOM requirements are generally based on the terms of the waiver.

The work-up for lisinopril performed at the ACS included a lot more testing than is included in the local work-up. As to the components of ACS Evaluation that are not included in this local work-up, basically the data collected in the study did not support efforts to continue these tests. Ophthalmologic testing can be included in the local work-up with a good optometry evaluation and should include screening for visual acuity and color vision. More testing should be based entirely on the needs of the individual aviator and can include a dilated fundus exam, a good external exam, a slit lamp evaluation motility testing and intraocular pressures. Contrast sensitivity, although a great tool for certain established diseases, did not reveal any consistent abnormalities with hypertensives on lisinopril. It is not recommended as part of the initial or annual requirement for lisinopril. Hearing tests are an annual exam done as part of the hearing conservation program, and no other requirements are necessary for lisinopril.

Vestibular testing at the Consult Service did not show any consistent abnormalities. Although some of the aviators had mildly abnormal tests, the results did not correlate with any clinical symptoms except in the aviator with recent surgery for an acoustic neuroma, who still had some residual vestibular symptoms at the time of his evaluation. There were also two aviators who complained of mild dizziness in the first week of lisinopril treatment. This was more of an orthostatic type of dizziness, however the vestibular testing showed mild phase abnormalities in one, and was normal in the other. Neither aviator had any symptoms at the time of testing. The testing would be more useful if it was possible to obtain baseline testing prior to the initiation of the drug and then a series of tests after the drug is initiated. Known ototoxic drugs such as gentamycin show a definite pattern of decrement in vestibular function when tested in this manner[3]. In an aviator who has symptoms referable to the vestibular system, VOR and optico-kinetics could be part of the work-up for the vestibular symptoms, but for screening they are not necessary.

The whole purpose of the psychological testing was to grossly and clinically screen for any effects of lisinopril on concentration or personality: the best method for doing this would be a pre-post-test evaluation using a combination of laboratory and clinical tests. No gross clinical findings with lisinopril were found based on the limits of this study. If there is a suggestion on the history taken by the flight surgeon that the hypertension or the medication has had effect on the mood, concentration or personality of the aviator, then further psychiatric and psychological evaluation and testing should be done. This

testing can be done initially with the aviator on the medication; then after at least three days off the medication, can be repeated. Lisinopril is not thought to carry the risk of rebound hypertension[35] so this should be a safe option. If available, any previous testing can be compared to these tests (EFS). Testing done after the aviator has been on a medication for at least 30 days may pick up subtle abnormalities, but they cannot be reliably attributed to either lisinopril, hypertension or both without some form pre-testing prior to the onset of either the medication or the hypertension. The flight surgeon history, if done well, can detect gross abnormalities in psychological functioning and lead to referral to the appropriate specialist if needed. As the data shows, the only disqualification attributable to a psychological disease (depression) was not felt to be related to lisinopril, but pre-dated the person even being placed on Lisinopril.

The detection of coronary artery disease is another broad area that has to be addressed due to the results of lisinopril study group. By far the bulk of the aviators disqualified from flying duty as a result of this study were due to coronary artery disease. As the data shows, 13 out of 94 evaluated were found have some degree of coronary artery disease. Of those, 10 were disqualified outright for the degree of coronary artery disease (SCAD), and two were disqualified as a result of MCAD plus another diagnosis (1 had V-Tach, the other had a blood pressure not controlled by lisinopril). Based on this finding alone there is sufficient reason to add coronary artery disease testing to the local protocol. These aviators would not have been detected until they suffered an event. At least one aviator did have a myocardial infarction that required bypass surgery since being disqualified for SCAD.

The medical literature on testing asymptomatic persons for CAD is scant, but does support this approach. Kruyer has stated that the incidence CAD in all aviators is about "five percent certainly less than 10 percent"[32]. The lisinopril study shows the prevalence in a selected population of about 14 percent. Although there have been no Class A aircraft accidents directly attributable to either hypertension or the treatment of hypertension, there is historical evidence of CAD causing aircraft accidents[33,39]. There are also studies that document CAD in young military men from both the Korean War and the Vietnam War[14,40]. Although the incidence of CAD has decreased since then, it has not gone away.

The use of the exercise treadmill test is one screening method that, although far from perfect, is probably the best test available. The sensitivity and specificity of this test when used alone as an indicator for catheterization was shown in the preceding discussion (46% sensitivity, 82% specificity). Specificity for the entire group of 94 aviators is more difficult to calculate since we do not usually pursue negative tests; the false negative rate can only be guessed at. The false negatives would be those who went to cardiac catheterization for either a positive thallium or positive fluoroscopy and had disease detected despite a negative ETT. There was a total of 7 aviators with a negative treadmill who underwent cath for other positive noninvasive tests and had gradable CAD. This means that if we had used only the treadmill to screen the members of this study, we would have missed 7 cases of disease (6 were SCAD) In this study we also had one aviator who had all screening tests normal but later had chest pain with a 90 percent LAD

lesion discovered. Whether or not having gradable diseases is enough to call the treadmill positive is debatable and was addressed by Dr. Paul Celio in this excerpt from a letter to the Surgeon General's Office in August, 1991:

"How do we initially discover aircrew coronary lesions? Most USAFSAM occupational catheterizations are due to abnormal noninvasive tests- abnormal treadmill or Thallium tests consistent with reversible ischemia. When we find a 75%, or 90% or 50% obstruction, we are generally sure that this anatomy explains the reversible ischemia. When we find 20% or 30% lesions, in an aircrew member who went to cath because of abnormal ischemic tests; are we sure that the lesions and the observed ischemia are unrelated? Based upon available data in coronary physiology and coronary reserve phenomena, we know that "stiff" nondilatable coronary vessels due to generalized atherosclerosis, in the absence of measurable obstructions, can produce ischemia. From flow mapping with digital subtraction angiography, coronary flow reserve has been shown to be decreased in some subjects with ST segment depression on exercise testing, in the absence of fixed, measurable obstructions. In contemporary testing we now know enough to not blandly dismiss such exercise tests as "false positives". We certainly now know enough not to assume that 20% to 39% lesions, in a subject who went to cath because of ischemic testing, are unrelated to the ischemic tests. Coronary lesions are quite complex, and a simple luminal narrowing tells the story very poorly. When we do find 20% to 30% lesions in subjects with ischemic testing, we should not dismiss them. In some aircrew, it may be that the relationship between the lesions and the noninvasive tests is "true, true, unrelated". However, since almost all cathed aircrew go to cath because of ischemic tests, it would be a very poor bet to assume that such lesions and the accompanying vasculopathy are unrelated to the observed electrocardiographic or scintigraphic changes"

The use of coronary artery fluoroscopy as a screening method is also fraught with difficulty. There is a lot of experience with this technique at the ACS, but not much among radiologists in the field. The method is described in a Loecker's paper, and sensitivity and specificity there were noted as well(66.3% sensitive, 77.6% specific)[36]. The Army uses coronary artery fluoroscopy as a screening method for evaluation of aviators who have risk factors for coronary artery disease. For some time the ACS did cardiac catheterization on Army aviators with positive fluoroscopy. This enabled the ACS to compare its findings on fluoroscopy with those of the field radiologists doing this test for these Army aviators. They actually compared well. Any positive CAF in the field will need to go to the ACS for further work-up and a repeat CAF is part of that work-up. Unless the ETT is positive there will be no way to judge the accuracy of negative CAF exams in the field.

Another method for detecting calcification in the coronary arteries is ultra-fast CT. At this time there is not enough experience with this method and it is not readily available at some sites. It is also expensive to use as a screening test. There's not sufficient experience to know when to perform cardiac catheterization on someone with a positive test. It does have promise and, with experience might one day replace the coronary artery fluoroscopy.

Thallium scintigraphy is the third test used at the ACS to determine eligibility for cardiac catheterization. The ACS uses a formula to determine when an individual with positive screening tests should proceed to cardiac catheterization. This formula is called the MACADE formula. It is part of an established approach to determine the need for cardiac catheterization in an asymptomatic aviator with positive screening tests for coronary artery disease. A letter to the Surgeon General describing the MACADE formula is included as attachment 9.

Test or Variable	Results of Cardiac Cath		Fisher's Exact Test	Interpretation
	No CAD	CAD		
ABN EKG	1/11	2/13	1	NS
ABN TREADMILL	2/11	6/13	0.2108	NS
ABN FLUOROSCOPY	7/11	10/13	0.6591	NS
ABN THALLIUM	3/11	3/13	1	NS
FAMILY HISTORY POS	7/11	3/12	0.0995	NS
SMOKING HX	1/11	2/13	1	NS
NO EXERCISE	1/11	1/13	1	NS
PRIOR THIAZIDE USE	6/11	11/13	0.1819	NS
TIME NOT TREATED	4/11	2/13	0.3572	NS
	No CAD	CAD	T-TEST	Interpretation
CHOLESTEROL	226.64	209.46	0.2262	NS
HDL	41.09	42.62	0.6885	NS
LDL	154.64	139.92	0.2441	NS
CHOL/HDL RATIO	5.76	5.08	0.2263	NS
AGE	43.55	45.54	0.1598	NS
DOSE OF LISINOPRIL	16.14	19.23	0.5397	NS
YEARS OF HBP	9.32	10.01	0.8016	NS
BODY FAT PER CENT	20.03	19.88	0.9279	NS
INITIAL BP AT ACS				
SYSTOLIC	125.55	138.46	0.0037	SIGNIFICANT
DIASTOLIC	83.45	89.92	0.0432	SIGNIFICANT

Figure 3 Rates and Means for Various Factors: "No CAD" vs. "CAD" on Cath

There was an attempt to use CAD risk factors to try to develop a subgroup within this group of hypertensives to test for coronary artery disease. Figure 3 summarizes a comparison of factors in the individuals who underwent cardiac catheterization. The small numbers in this study did not achieve any ability to separate out a subgroup with an increased risk for CAD based on traditional risk factors. As shown in Figure 3, the initial blood pressure taken at entry to the ACS was significantly higher in the group of 13 who had CAD on cath vs. the 11 who did not have gradable disease on cath. This was the only factor that showed any statistical difference between the two groups. Interestingly, the group that had CAD had better lipid means across the board compared to the group without CAD. This group also had fewer individuals with a positive family history for CAD. This highlights how difficult it was to use risk factors in this subgroup to try to select those with the highest likelihood of having gradable disease on cath. The "Time not Treated" entry in this figure lists the number of individuals from each group who had a period of time after they were identified as being hypertensive when they were not treated. This was initially thought to be a risk for CAD in the study group but was not different between the two groups. A positive family history for CAD was defined by NCEP guidelines[49]. Active smoking was actually quite rare in this group with only three active smokers of 94 examined; none of these three went to cath. Twenty-two had a previous history of smoking, but 12 out of them had quit 10 or more years prior to their evaluation. In figure 3 those listed as positive for smoking were the former smokers who had at least a 20 pack-year history and had quit less than 10 years prior to their cath. It is important to encourage the aviator to quit smoking since this is one of the few modifiable

risk factors. Family history of coronary artery disease as defined by the NCEP guidelines was found positive in 26.6% of the whole group of 94 aviators

As an example, one aviator who was found a have a 90 percent LAD lesion had negative treadmill, thallium, and fluoroscopy testing. His total cholesterol was 201 and his HDL was 53 yielding a ratio of 3.8 and an LDL of 125. He had a negative family history for coronary artery disease. Another aviator with a total cholesterol > 300, an HDL less than 35, and a positive family history who had a positive treadmill and fluoroscopy was negative on catheterization. There was no single risk factor or collection of risk factors that clearly separated out a subgroup with a higher risk for gradable CAD.

CONCLUSION

The results of the lisinopril study have been used to generate a new approach to the local evaluation and treatment of hypertensive USAF aviators. In order to adopt a local work-up, some tests were added to the pre-existing algorithm approach presented in AFI 48-132. The new tests include an echocardiogram, and in a selected group, exercise treadmill testing and coronary artery fluoroscopy. This approach is not that dissimilar to the approach for screening for CAD used by the US Army.

For high performance aviators, centrifuge testing should still be performed until we have sufficient numbers to satisfy a 95% confidence that the risk of missing a true problem with G tolerance is less than 5%. Completion of an additional 38 aviators should fulfill this criteria. A new protocol for G tolerance testing is proposed which should make this process less troublesome. Follow-up evaluations need to be performed at least annually with echo and CAD testing performed at three to five year intervals. Attachment 10 summarizes the USAF approach to hypertension in aviators.

REFERENCES

1. Agewall S, Wikstrand J, Samuelsson O, et al. The Efficacy of Multiple Risk Factor Intervention in Treated Hypertensive Men During Long-term Follow Up. J Intern Med 1994;236:651-659.

2. American Public Policy Position Paper. Recommendations for routine blood pressure measurement by indirect cuff sphygmomanometry. Amer. Journ. of Hypertension 1992; 5:207-209.

3. Amery A, Birkenhager W, Brixko P, et al. Mortality and Morbidity Results from the European Working Party on High Blood Pressure in the Elderly Trial. Lancet 1985;1:1349-1354.

4. Amroliwalla FK. Angiotensin converting enzyme (ACE) inhibitors in hypertensive aircrew. Aviat. Space Environ. Med. 1994; 65: 1054-7.

5. Booze CF. Prevalence of disease among active civil airmen. FAA Office of Aviation Medicine. AM-89-2. October 1988.

6. Burt VL, Whelton W, Roccella EJ, Brown C, Cutler JA, Higgins M, Horan MJ, Labarthe D. Prevalence of hypertension in the US adult population. Results of the third national health and nutrition survey, 1988-1991. Hypertension. 1995; 25:305-313.

7. Cameron HA, Higgins TJ. Clinical experience with lisinopril; observations on safety and tolerability. J. Hum. Hypertens. 1989;3:177-86.

8. Celio PV. Aeromedical disposition of arrhythmias and electrocardiographic findings in aircrew. In Cardiopulmonary Aspects in Aerospace Medicine. AGARD-LS-189. 1993 p. 5.1-5.9.

9. Cinotti GA, Bossini A, Cagli V, Corea L, DiVeroli C, Morabito S, Pierucci A, Porcellati C, Savino K, Timio M. Multicenter clinical study of the antihypertensive activity of lisinopril. Minerva Med. 1989;80(1):53-63.

10. Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA, Godwin J, Qizilbash N, Taylor JO, Hennekens CH. Blood Pressure, Stroke, and Coronary Heart Disease. Part 2, short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. Lancet 1990;335:827-838.

11. Croog SH, Levine S, Testa MA, et al. The effects of antihypertensive therapy on the quality of life. N Engl J Med 1986;314:1657-1664.

12. Cyr DG, Harker, LA. Vestibular Function Tests. In Ear and Cranial Base. p 2670-6.

13. Dahlof B, Lindholm LH, Hansson L, et al. Morbidity and Mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). Lancet 1991;338:1281-1285.

14. Enos WF, Holmes RH. Coronary disease among United States soldiers killed in action in Korea. JAMA 1953;152:1090-1093.

15. Espinel CH, Williams JL, Coughlin SS. Enalapril and lisinopril in the treatment of mild to moderate essential hypertension. Clin Ther. 1990;12(2):181-90.

16. Frimodt-Moeller J, Poulsen DL, Kornerup HJ, Bech P. Quality of life, side effects, and efficacy of lisinopril compared with metoprolol in patients with mild to moderate essential hypertension. J. Hum. Hypertens. 1991;5(3):215-21.

17. Gilbert BW. Ace inhibitors and regression of left ventricular hypertrophy. Clin. Cardiol. 1992;15(10):711-4.

18. Hegeland A. Treatment of mild hypertension: a five year controlled drug trial, the Oslo Study. Am J Med. 1980; 09:725-732.

19. Herbert PR, Moser M, Mayer J, Glynn RJ, Hennekens CH. Recent evidence on drug therapy of mild to moderate hypertension and decreased risk of coronary heart disease. Arch Intern Med. 1993;153:578-581.

20. Herpin D, Conte D. Assessment of the antihypertensive effect of lisinopril using 24-hour monitoring. Journ of Hum Hyperten. 3: 11-15. 1989.

21. Hickman JR, Tolan GD, Gray GW, Hull DH. Clinical Aerospace Cardiovascular and Pulmonary Medicine. In Fundamentals of Aerospace Medicine. DeHart RL ed. Williams and Wilkins 1996. pp. 501-503.

22. Hull DH. Arterial hypertension and the aviator. In Cardiopulmonary Aspects in Aerospace Medicine. AGARD-LS-189. 1993 p. 15.1-15.7.

23. Hull DH. Mild hypertension. Aviat. Space Environ Med. 1985;56:304-9.

24. Hull DH, Wolthius RA, Triebwasser JH, McAfoose DA. Treatment of hypertension in aviators: A clinical trial with aldactazide. Aviat. Space Environ. Med. 49(3): 503-511. 1978.

25. Hypertension Detection and Follow-up Program Cooperative Group. The Effect of Treatment on Mortality in "Mild" Hypertension. Results of the Hypertension Detection and Follow-up Program. N Engl J Med 1982;307:976-980.

26. Israili ZH, Hall WD. Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy: a review of the literature and pathophysiology. Ann. Intern. Med. 1992;117(3):234-42.

27. Jain M, Armstrong L, Hall J. Predisposition to and late onset of upper airway obstruction following angiotensin-converting enzyme inhibitor therapy. Chest. 1992;102(3):871-4.

28. Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI). NIH Publication No. 98-4080. November 1997.

29. Julius S, Gupta R. Angiotensin converting enzyme inhibitors and the progress of antihypertensive therapy. Journ of Hypertens 1989. 7 (suppl 5):S23-S27.

30. King WH, Lancaster MC, Cloyd DE. Antihypertensive drug therapy in USAF flying personnel. Aviat. Space Environ. Med. 46(4): 436-440. 1975.

31. Kochar MS, Bolek G, Kalbfleisch JH, Olzinski P. A 52-week comparison of lisinopril, hydrochlorothiazide, and their combination in hypertension. J. Clin. Pharmacol. 1987;27(5):373-7.

32. Kruyer WB. Screening for asymptomatic coronary heart disease. In Cardiopulmonary Aspects in Aerospace Medicine. AGARD-LS-189. 1993 p. 2.1-2.5.

33. Li G. Pilot-related factors in aircraft crashes: A review of epidemiologic studies. Aviat Space Environ Med. 1994; 65:944-52.

34. Lind L, Pollare T, Berne C, Lithell H. Long-term metabolic effects of antihypertensive drugs. Am Heart J 1994;128:1177-83.

35. Lisinopril for Hypertension. Medical Letter 1988;30:763.

36. Loecker TH, Schwartz RS, Cotta CW, Hickman JR. Fluoroscopic coronary artery calcification and associated coronary disease in asymptomatic young men. J Am Coll Cardiol 1992;19:1167-72.

37. MacMahon SW, Cutler JA, Furberg CD, Payne GH. The effects of drug treatment for hypertension on morbidity and mortality from cardiovascular disease: A review of randomized controlled trials. Prog in Cardiovasc Dis. Vol XXIX. No 3, Suppl 1, 1986: pp 99-118.

38. Maschio G, Alberti D, Janin G, et al. Effect of the angiotensin-converting-enzyme benazepril on the progression of chronic renal insufficiency. N Engl J Med 1996;334:939-45.

39. McCormick TJ, Lyons TJ. Medical causes of In-Flight Incapacitation: USAF experience 1978-1987. Aviat Space Environ Med. 1991; 62:884-7.

40. McNamara JJ, Molot MA, Stremple JF, Cutting RT. Coronary Artery Disease in Combat Casualties in Vietnam. JAMA. 1971;216:1185-1187.

41. Mehta J, Lopez LM, Thorman AD. Lisinopril versus lisinopril plus hydrochlorothiazide in essential hypertension. Am. J. Cardiol. 1988;61(10):803-6.

42. Neaton JD, Grimm RH, Prineas RJ, et al. Treatment of Mild Hypertension Study. JAMA 1993;270:713-724.

43. Paul MA, Gray GW. The effect of captopril on +Gz tolerance of normotensives. Aviat. Space Environ. Med. 1992;63:706-8.

44. Pfaff JR, Newberry PD. Effect of hydrochlorothiazide on +Gz tolerance in normotensives. Aerospace Med. 43(11): 1225-1229. 1972.

45. Physicians' Desk Reference. 1998, 52nd ed., Ronald Arky. Medical Economics Co., Montvale, NJ, p 1729-33.

46. Schmeider RE, Martus P, Klingbeil A. Reversal of Left Ventricular Hypertrophy in Essential Hypertension. JAMA 1996;275:1507-1513.

47. SHEP Cooperative Research Group. Prevention of Stroke by Antihypertensive Drug Treatment in Older Persons with Isolated Systolic Hypertension. JAMA 1991;265:3255-3264.

48. Stamler J, Stamler R, Neaton JD. Blood pressure, systolic and diastolic, and cardiovascular risks. US population data. Arch Intern Med. 1993; 153:598-615.

49. Summary of the second report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel II). JAMA 1993;269:3015-23.

50. Sytkowski PA, D'Agostino RB, Belanger AJ, Kannel WB. Secular trends in long-term sustained hypertension, long-term treatment, and cardiovascular mortality. The Framingham Heart Study 1950 to 1990. Circulation. 1996;93:697-703.

51. The Multiple Risk Factor Intervention Trial Group. Mortality Rates After 10.5 Years for Participants in the Multiple Risk Factor Intervention Trial. JAMA 1990;263:1795-1801.

52. Webb JT, Oakley CJ, Meeker LJ. Unpredictability of fighter pilot G tolerance using anthropometric and physiologic variables. Aviat. Space Environ. Med. 1991;62(2):128-35.

53 Webster KH, Triebwasser JH, Lancaster ML. Rationale and approach to drug evaluation for use in flying personnel. Preprints of 1972 Annual Scientific Meeting, Aerospace Medical Association, p. 79-81.

54. Whinnery JE. Acceleration tolerance of asymptomatic aircrew with mitral valve prolapse. Aviat. Space Environ. Med. 1986;57:986-92.

55. Whinnery JE. On the theory of acceleration. Warminster, PA: Naval Air Development, 1988; NADC Report No. 88088-60.

56. Wirebaugh SR, Spencer GA, McIntyre TH. Lisinopril use in a large military medical center. Military Medicine, 162, 2:113, 1997.

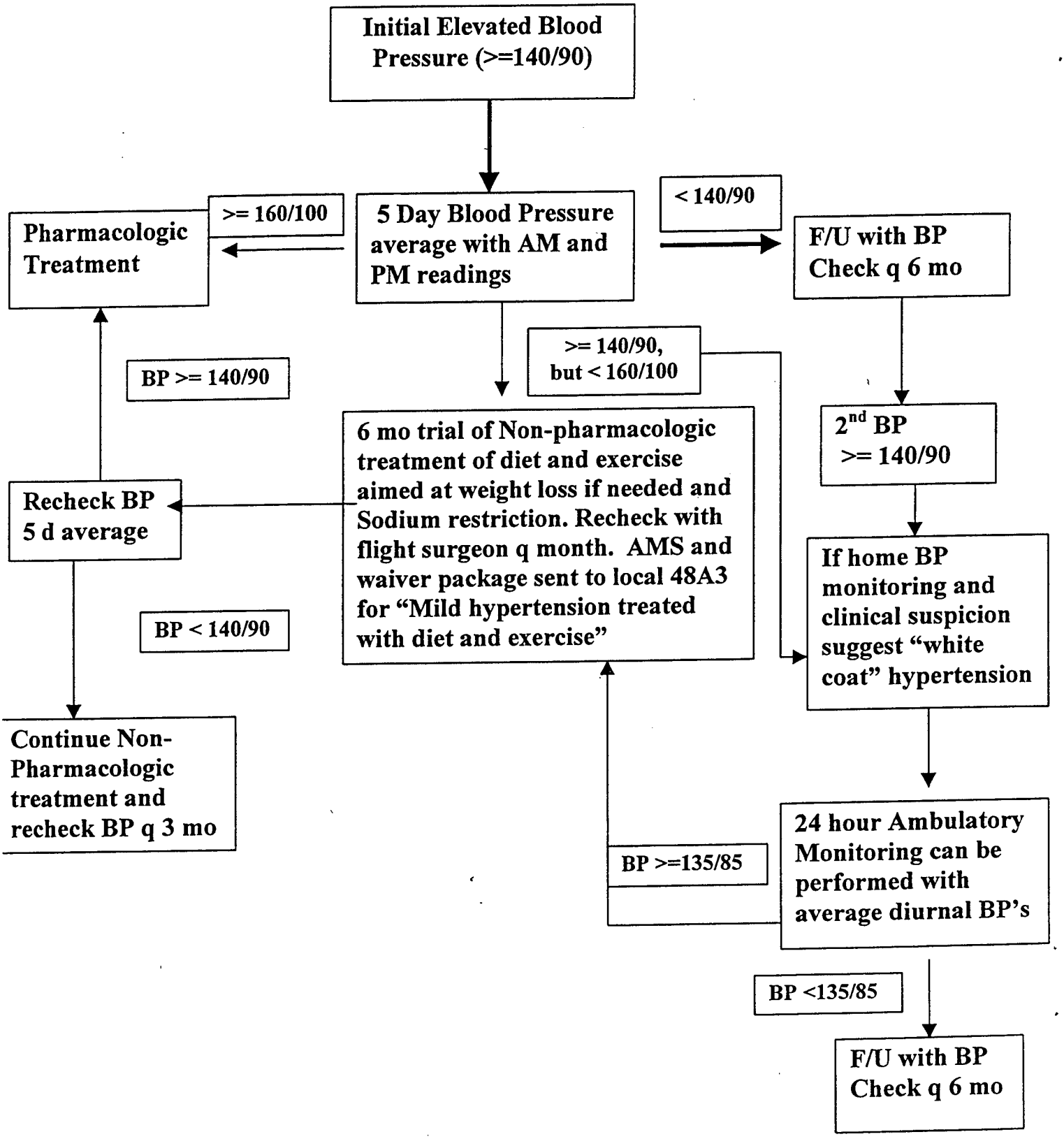
57. Zanchetti, A. The clinical role of angiotensin converting enzyme inhibitors in antihypertensive therapy in the 1990's. Journ of Hyperten 1989, 7 (suppl 5):S37-S40

THIS PAGE INTENTIONALLY LEFT BLANK

ATTACHMENTS

Attachment 1. Flowcharts for the Treatment of Hypertension in USAF Aviators
Attachment 2 Research Protocol for the Evaluation of Medical Waiver Requirements for the Use of Lisinopril in USAF Aviators
Attachment 3 AFI 48-132 USAF Waiver Guide: Hypertension
Attachment 4 Coronary Primary Prevention Program (Memo from Col Jeb Pickard)
Attachment 5 ACS Modified Balke Exercise Treadmill Test
Attachment 6 Guidelines for Completing Aeromedical Summaries
Attachment 7 AFI 11-404
Attachment 8 New Lisinopril Centrifuge Protocol
Attachment 9 MACADE Letter
Attachment 10 Lisinopril Local Evaluations Letter

DIAGNOSIS AND NON-PHARMACOLOGIC TREATMENT OF HYPERTENSION IN AIRCREW



Coronary Artery Disease Screening in Hypertensive Aircrew

Risk Factors
LDL>=160
HDL <=35
Current smoker
+Fam Hx for CAD*
HDL >=60 is -1

Hypertensive on medication,
Male, >= age 40
Female >= age 50

Exercise Treadmill Test
Coronary Artery Fluoroscopy
(results sent to ACS)

If either is positive, to ACS for eval for cath

If negative, risk factor modification should be continued with re-eval of status in 3 years

***NCEP Guidelines**
Fam Hx pos if hx of CAD in 1st degree male relative 55 or younger, 1st degree female relative 65 or younger

Pharmacologic Treatment of Hypertensive Aircrew

All hypertensive aircrew worked up and treated locally

↓

History and Physical: aimed at detecting end-organ damage and signs and symptoms of secondary causes of hypertension

↓

Lab: CBC, Lytes, BUN, creatinine, Glucose, Ca, Uric Acid, LFT's , urinalysis. Other lab as indicated. EKG, CXR, echocardiogram

↓

Start Rx with either lisinopril or diuretic. * After 30 days, repeat a five day AM & PM BP and repeat all lab with a lipid panel. If average BP <140/90, no side effects and lab OK, may apply for waiver.** Send copies of lisinopril package to Brooks AFB with consent for use of data

→ **All high performance aviators on lisinopril require a monitored centrifuge ride at Brooks prior to applying for waiver

↓

Initial F/U q 1 mo X3 then q 3 mo for 1st year. At end of first year recheck lab (CBC,lytes,BUN,creatinine,U/A) and ECG. AMS with 5 day BP average, above lab and ECG should be submitted to waiver authority with copy to Brooks (with consent). Thereafter, q 6mo check with annual submission of waiver package

*For lisinopril: check BUN and creatinine 3 days after starting Rx. If creatinine rises >1mg/dl and persists, D/C lisinopril and W/U for renovascular HBP

Appendix C: *Research Protocol for the Evaluation of Medical Waiver Requirements for the Use of Lisinopril in USAF Aircrew*

Armstrong Laboratory
Clinical Sciences Division

Research Protocol for the Evaluation of Medical Waiver Requirements for the Use of Lisinopril in USAF Aircrew

1. **Project-Task-Work Unit**: 7755-27-23

2. **Principal Investigator**:

Robert Johnson, Maj, USAF, MC, SFS
Chief, Clinical Research Coordination Center
Clinical Sciences Division
Aerospace Medicine Directorate
Armstrong Laboratory
Human Systems Division
Brooks AFB TX 78235-5301
Phone: DSN 240-3647

3. **Associate Investigators**:

Roger U. Bisson, Lt Col, USAF, MC, SFS (DSN 240-3464)
Paul V. Celio, M.D., F.A.C.C. (DSN 240-3242)
William G. Jackson, Jr, M.S., (DSN 240-2285)

4. **Medical Consultant**:

Designated Flight Surgeon
USAFSAM/AF Department of Areospace Medicine (DSN 240-2844)

5. **Contractor**: Not applicable

6. **Project Objectives**: To determine if aviators on lisinopril for the treatment of primary hypertension require individual centralized evaluation at the Aeromedical Consultation Service or can clinical criteria be identified to establish Local Flight Surgeon's Office medical waiver evaluations.

Related questions are:

a. How long after beginning lisinopril therapy should aviators be monitored to detect 95% of the aeromedically significant side effects?

b. Can aviators on lisinopril for the treatment of hypertension be medically evaluated locally and aeromedically waived for flight duties or does detection of some medication

effects (including performance such as acceleration tolerance for high-performance aviators) require pre-waiver evaluation which are best evaluated at the Clinical Sciences Division or otherwise not locally available to the referring base.

7. **Background**: Lisinopril is a long-acting oral preparation angiotensin-converting enzyme (ACE) inhibitor. Lisinopril received Food and Drug Administration approval for the treatment of hypertension in 1987 and has been widely and safely used for that indication since that time. The beneficial effects of lisinopril in hypertensives result primarily from suppression of the renin-angiotension-aldosterone system. Inhibition of ACE results in decreased plasma angiotensin II which leads to decreased vasopressure activity and to decreased aldosterone secretion. Lisinopril is absorbed in the gastrointestinal tract and is metabolically active. It is excreted unchanged by the kidney. Studies in rats indicate that lisinopril crosses the blood-brain barrier poorly. Radioactively tagged lisinopril in pregnant rats was found in the placenta but not in the fetuses.

Large clinical trials of lisinopril established its effectiveness for the treatment of hypertension (n = 3,270).[5,15] Metabolic effects appear to be minimal and no renal failure has been noted with prolonged therapy (n = 1,104).[20,26] ACE inhibitors as a class of drugs decrease systemic vascular resistance, blood pressure and improve cardiac functioning while maintaining or enhancing perfusion of the kidneys, brain and heart.[30] ACE inhibitor therapy decreases left ventricular hypertrophy.[11] Cinotti, et al, reported that the incidence of side effects were limited in a clinical trial of 100 subjects and that no case required withdrawal of lisinopril.[6]

In comparison clinical trials for the treatment of hypertension, lisinopril proved more effective than hydrochlorothiazide in a 52-week study[21] and demonstrated effectiveness in another study without major side effects reported.[22,24] In a double-blinded, randomized, parallel-group multicenter trial of 340 patients with hypertension, the side effect profile of lisinopril was not different from that of the placebo group and adverse effects were few and mild.[29]

Some laboratory abnormalities have been reported. One study reports the rare occurrence of glycosuria;[23] another study reports an increased blood urea nitrogen, serum creatinine and plasma potassium (n > 1,000) but notes that these effects were fewer than other antihypertensive medication.[25] In another study, Espinel, et al, studied 97 subjects, 47 on lisinopril, and reported no laboratory abnormalities.[7]

Systemic effects of lisinopril have been evaluated clinically. Angioedema of the face and neck is the most severe reported clinical complication. Jain reports on five cases of this untoward side effect, four in patients treated with enalapril, an ACE inhibitor, and one in a patient treated with lisinopril. Obesity, previous head and neck surgery or a history of intubation appears to be a significant cofactor in these patients.[19] Cough has been described as an annoying side effect of all ACE inhibitors and usually appears within one hour to one week after beginning therapy. Incidences of this side effect are similar to all the drugs in the class of ACE inhibitors.[2,17,34] Overall quality of life was studied by Frimodt-Moeller, et al, using the General Health Questionnaire. They noted the quality of life was significantly improved two months after discontinuing thiazide therapy and beginning lisinopril therapy and there were fewer withdrawals on lisinopril as compared to metoprolol (a beta-blocker) (n = 360).[9,24]

The effects of antihypertensive treatment on G tolerance is of significant aeromedical concern.[3,12] This has not been well elucidated in the literature. Paul and Gray studied seven

normotensive and randomized them to placebo or captopril, an ACE inhibitor, and evaluated their +Gz tolerance. They found decreased tolerance in the treated subjects.[27] This is the expected result in normotensives with a drug-induced decreased systemic vascular resistance.[14,16,35] This will be the first study of adequately treated hypertensives with +Gz tolerance testing. Webb, et al, described the unpredictability of fighter pilot's G tolerance using anthropometric and physiologic variables. They studied 1,343 high-performance pilots and found that relaxed G tolerance was inversely correlated with age, weight and diastolic blood pressure. Correlation coefficents either as single variables or in a multivariable model failed to demonstrated a value of greater than 0.35. The only consistent prediction of G tolerance was the anti-G straining maneuver.[32] Whinnery looked at the medical consideration of G-LOC. He concluded that there is no indication that G-LOC episodes have any associated long-term or persistent psychophysiological sequelae.[34] The potential exists that lisinopril therapy affects +Gz tolerance.

8. **Relevance to the Air Force**: Air Combat Command and Air Force Materiel Command have requested Armstrong Laboratory to study an ACE inhibitor for the treatment of hypertension in aviators. ACC noted that in 1990 they had 55 aviators with hypertension who were not controlled or poorly controlled with the Hydrochlorothiazide (HCTZ) diuretic. Air Force wide it is expected that there are greater than 200 hypertensive aviators who could benefit from lisinopril therapy. USAF/SGPA requested that a plan be developed to evaluate aviators on a medication other than HCTZ for waiver. A plan to evaluate those aviators was developed by the Clinical Sciences Division (attachment 2). This protocol will delineate an organized scientific plan to obtain, organize, analyze and then report the information gathered during the course of aeromedical occupational examination at the Clinical Sciences Division of Armstrong Laboratory to the USAF Surgeon General for a refinement of regulatory directives.

Currently, there are only two medications available to local flight surgeons for the treatment of hypertension. Aviators controlled with HCTZ may obtain a waiver after a short period of grounding and a local evaluation. If local flight surgeons desire a different medication, a centralized evaluation at the Clinical Sciences Division is required. Lisinopril is the only other antihypertensive medication currently considered for waiver.

Thiazide diuretics are the only anti-hypertensives avilable locally for the treatment of primary hypertension in USAF aircrew. Diuretic therapy was the medical standard of care for the treatment of hypertension when that policy was instituted. Currently, there are many new classes of medication to treat this condition. Thiazide diuretics' main effect is decreasing intra-vascular volume, and often have untoward side effects of increasing cholesterol and producing electrolyte imbalances.

9. **Impact Statement**:

If this study is not done :

a. Hypertensive aviators will continue to be placed on HCTZ or they will need to recieve an evaluation at the Clinical Sciences Division.

b. Alternative therapy to thiazide or thiazide combinations will not be locally available. The untoward side effects of thiazide will be present in some aviators on thiazides.[36] Medical choices to treat aviators for hypertension will be limited to diuretic therapy

alone, this will result in fewer aviators flying on waiver and the loss of trained and experienced aviators for the Air Force.

10. **Experimental Plan**:

a. Study Design: This research is a prospective cohort study using established controls. This is an observational study. This study does not evaluate the efficacy or the effectiveness of the treatment of hypertension with lisinopril. The six hypotheses listed below result from aeromedical clinical concerns and literature review. All of the study subjects will be entered after their hypertension is therapeutically controlled. Data collected from participants during aeromedical occupational evaluation of aviators on lisinopril will be collected, organized, analyzed and reported. Systematic analyses of the data provided by aeromedical evaluations will provide a basis for quantativlely driven aeromedical recommendations regarding future regulatory guidance concerning USAF aviators on lisinopril.

Control data used in the analysis of this study could be considered external, since the control data were not collected under the supervision of the investigator. External control data, if taken from other institutions, often adds to the potential of, difficult to account for, bias adding to the study. Comparing different populations on a single or multiple variables may result in systematic error (bias) which cannot be well controlled for in even the most rigorous statistical analyses. The control data utilized in this study is retrospective data from our organization.

Control data used in our analysis is robust and from similar populations; USAF aviators evaluated at the Clinical Sciences Division and recommended to return to fly. Acceleration data are from published acceleration tests derived from normotensive aviators evaluated on the Brooks AFB centrifuge. This control group is arguably the best control group since it is a random subset of healthy USAF aviators, the information was gathered at this institution, and there is limited potential for confounding due to medication or other potentially biasing effects. The acceleration performance question is not the effect or performance of the medication but rather the individual performance of the therapeutically controlled aviator compared to a normotensive qualified aviator.

The validity of our control data is strengthened since the information was collected at this institution in recent years. It is weakened somewhat due to the lack of randomization. Bailar writes in Medical uses of Statistics of the use of external control and states that five interrelated features can add to the strength of studies using external controls.[1]

"... (1) an intent by the investigator, expressed before the study, that the treatment will affect the outcomes reported; (2) planning of the analysis before the data are generated; (3) articulation of a plausible hypothesis before the results are observed; (4) a likelihood that the results would still have been of interest if they had been "opposite" in some sense; and (5) reasonable grounds for generalizing the results from the study subjects to a substantially broader group of patients."

This primarily deals with clinical trials but the cautionary role is useful in determination of validity issues in this study. The strength of this study is derived from the prospectively planned methodology and the appropriateness of the control group.

b. Limitations of this study: This study is designed to test the six hypotheses listed below. The possibility exists that there may be other parameters or clinical features missed by the focused examination. This study is designed to analyze the clinical data gathered during the Clinical Sciences Division occupational evaluation. Due to the relative smallness of the expected sample size, rare events will not be quantifiable.

c. Research questions to be investigated:

1) Are there detectable aeromedically significant vestibular abnormalities present in aviators with hypertension therapeutically controlled with lisinopril?

2) Are there detectable aeromedically significant audiometric abnormalities present in aviators with hypertension therapeutically controlled with lisinopril?

3) Do aviators with hypertension therapeutically controlled with lisinopril have an increased risk of aeromedically significant coronary artery disease?

4) Do aviators with hypertension therapeutically controlled with lisinopril have an increased risk of aeromedically significant ophthalmologic disorder?

5) Do aviators with hypertension therapeutically controlled with lisinopril who fly high-performance aircraft have a decreased G tolerance compared to normotensive aviators on no medication who fly high performance aircraft?

6) Do aviators with hypertension therapeutically controlled with lisinopril demonstrate laboratory abnormalities in blood and/or urine samples?

d. Testing: Evaluations at the Clinical Sciences Division: Aeromedical evaluations shall include an examination to identify medication side effects and to delineate and quantify selected performance testing: The clinical evaluation listed represents the battery of tests and observations currently required by USAF/AFMOA for the consideration of waiver for aviators on lisinopril for hypertension. This evaluation has been reviewed and was determined to be the aeromedical standard of care for hypertensive aviators on lisinopril evaluated at the Clinical Sciences Division by the Clinical Sciences Division Quality Assurance Committee.(attachment 2)

e. Subject pool: Potential Subjects: Lisinopril protocol subjects will be drawn from all consenting aviators who are evaluated at the Clinical Sciences Division for the treatment of hypertension with lisinopril. This study is open to all aviators evaluated, female and male.

All Clinical Sciences Division Evaluees on lisinopril will be offered inclusion in this study. The goals, purpose and expected duration will be discussed with them, their questions will be answered and if they agree to participate, the attached study consent form will be completed and signed (attachment 1).

f. Duration of the Study: The study is intended to be carried out over five years. Since the study is designed to test the study questions stated in Section 10.c of this protocol, the data will be analyzed semi-annually the first year and annually thereafter to determine approximately how many subjects will be required to adequately test each hypothesis and, if given the current rate of subject recruitment and follow-up, that number will be reached within the planned five-year duration of the study. The study will be terminated when this number is reached or, if data analysis by the investigators, it is statistically determined that the stated research question cannot be supported by the data. The study will be stopped if greater than 50% of aviators are denied waiver post ACS evaluation with an alpha error set at 0.05 and beta error of 0.20 (power = 0.80).

g. Statistical Methods: Three questions to which known answers might affect the continuation of all or parts of the Lisinopril study and which will be addressed statistically in this study are:

(1) Is the overall yield of waiverable aviators among the study subjects below 50%?

(2) For any particular cluster of tests (G-tolerance, coronary artery disease, etc.), is the prevalence of a disqualifying condition greater than or less than 5%?

(3) For any test that yields a continuous response, is the mean value for Lisinopril subjects different from the mean of aeromedically "normal" subjects?

The methods described below to answer these three questions could easily be adjusted to take into account other null hypotheses if so desired (such as 60% in Question 1).

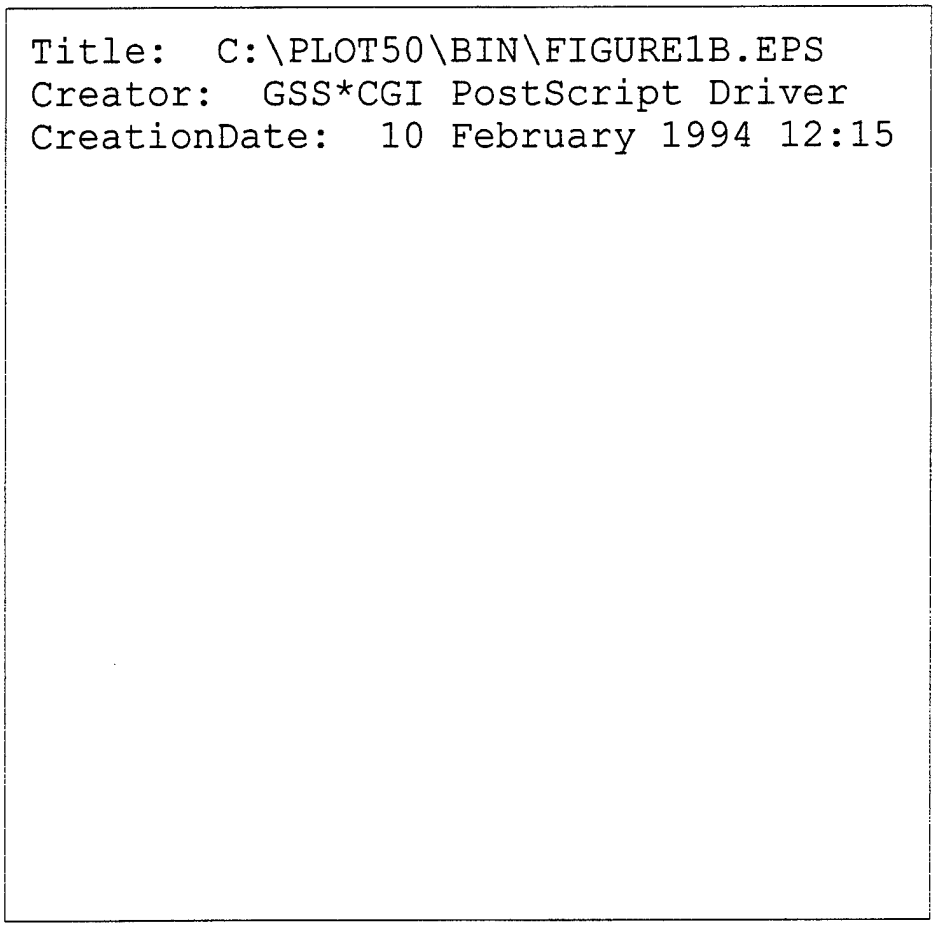


Figure 1. Power of five sequential stopping rules for accepting H_a: percent disqualified > 50%. Overall Type I error rate = 5%.

Figure 1 addresses power for a test of the null hypothesis (H_0) that the percent of subjects on Lisinopril who are found to be waiverable will be at least 50% vs. the 1-tail alternative hypothesis (H_a) that the percent not receiving waiver will exceed 50%. H_0 will be tested sequentially after 20, 40, 60, 80, and 100 subjects have completed the waiver process, and an unacceptably large number of disqualifications at any of these five steps will result in rejection of H_0. The five critical values for rejection are, respectively, 16 disqualifications out of the first 20 subjects, 28 of the first 40, 40 of the first 60, 51 of the first 80, or 63 of the first 100. The overall Type I error rate for the test does not exceed 5%. In terms of power, Figure 1 shows, for example, that if the overall disqualification rate is 70%, then the probability that H_0 will be rejected after 20 subjects is only about .23, but that probability rises to about .60 after 40 subjects and .80 after 60 subjects.

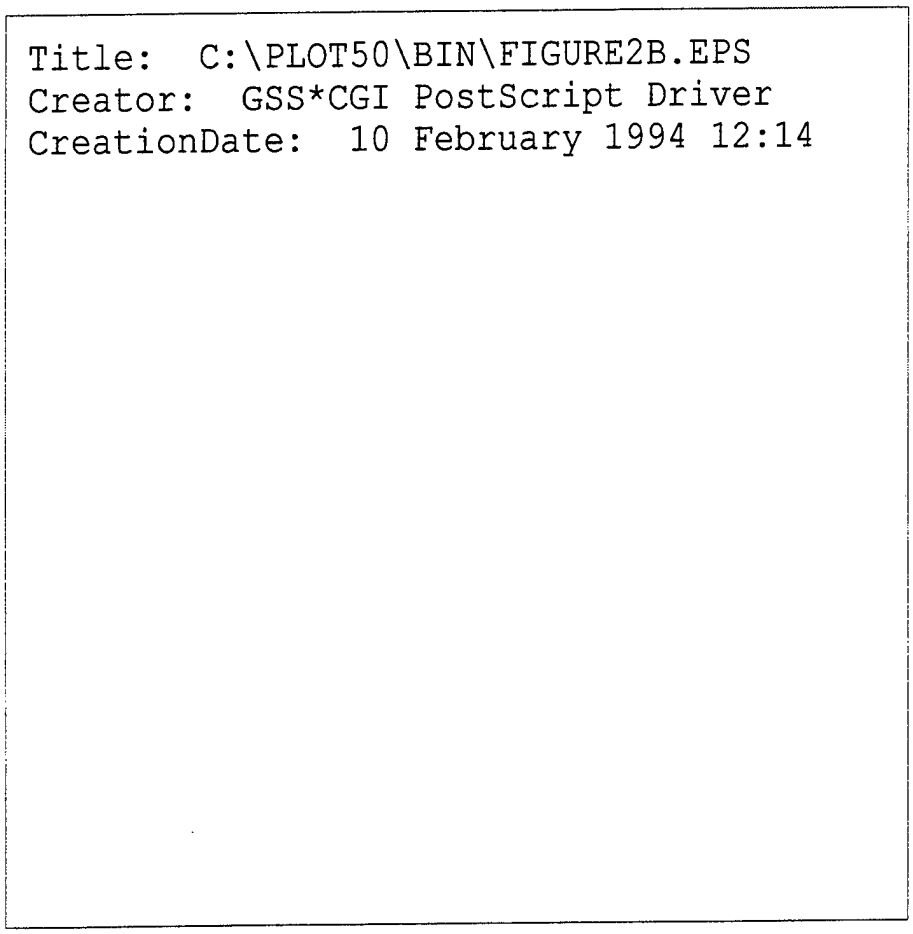


Figure 2. Power of five sequential stopping rules for accepting H_a: prevalence of disqualifying result on a particular test differs from 5%. Overall Type I error rate = 10%.

Figure 2 addresses power for a test of the null hypotheses (H_0) that the percent of subjects on Lisinopril found to be waiverable for a particular cluster of medical tests (such as the centrifuge, coronary artery disease, etc.) will equal 95% vs. the 2-tail alternative hypothesis (H_a) that the percent disqualified will differ from 5% (the assumed prevalence of abnormality among aviators not on Lisinopril). These tests will be 2-tailed so that rejection of H_0 can guide a decision to either discontinue or make permanent the particular cluster of exams on Lisinopril aviators seeking a waiver to fly. H_0 will be tested sequentially after 20, 50, 80, and 100 subjects have completed the waiver process. Too few or too many disqualifications at any of these four steps will result in rejection of H_0. The critical values that lead to a conclusion that the disqualification rate exceeds 5% are 4 (or more) disqualifications out of the first 20, 7 (or more) out of the first 50, 9 (or more) out of the first 80, and 11 or more out of the first 100. The critical value that leads to a conclusion that the disqualification rate is less than 5% is 1 disqualification of the first 100. The Type I error rate for this sequence of statistical tests for particular cluster of medical procedures is less than 10%. In terms of power, Figure 2 shows, for example, that if the disqualification rate for a related cluster of procedures is 20%, then the probability that H_0 will be rejected after 20 subjects is about .40, but the probability rises to over .80 after 50 subjects and over .95 after 80 subjects.

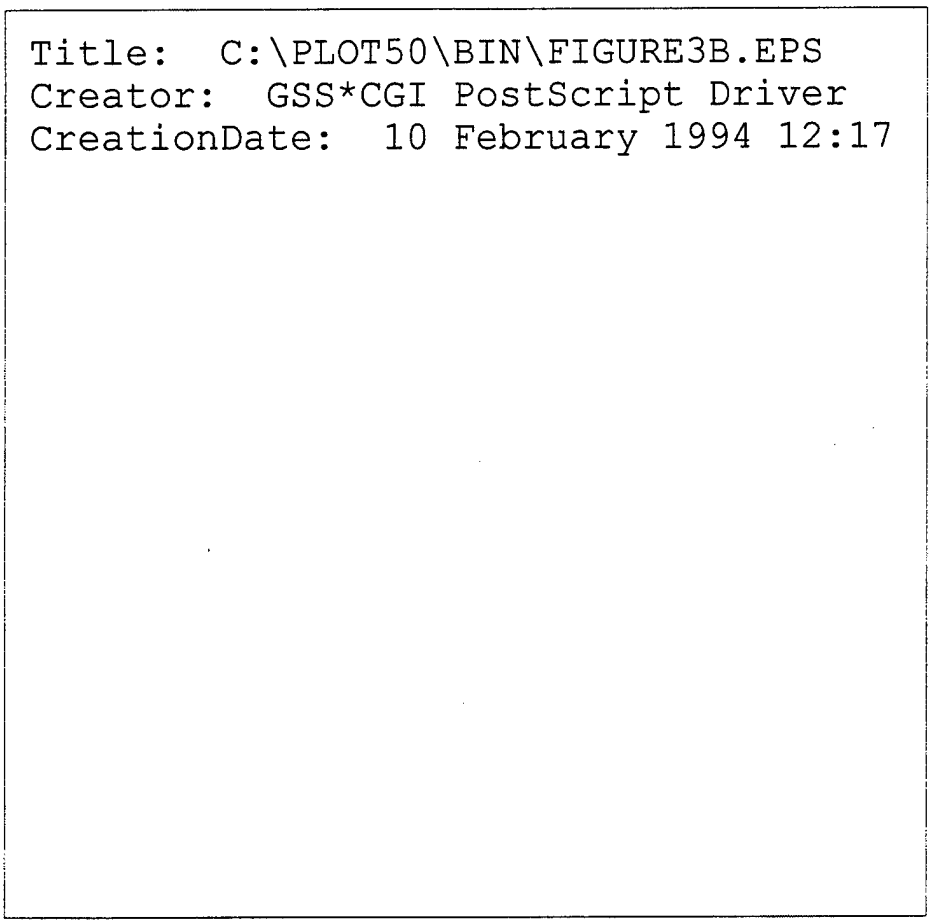


Figure 3. Power curves for 2-tail, unpaired t-tests with group sample size of 20, 50, and 100, and Type I error rate = 5%.

Figure 3 shows power curves for 2-tail unpaired t-tests with equal sample sizes of 20, 50, and 100 observations for testing a null hypothesis (H_0) that the mean response for Lisinopril subjects on a particular procedure (such as G-tolerance for the rapid-onset run) does not differ from the mean value for "normal" subjects. "Normal" here will generally mean a waiverable population of flyers seen historically at the Armstrong Laboratory. The mean difference is measured in units of standard deviations since that will change for each procedure. The range of differences is from -1.5 to +1.5 standard deviations, which represents a wide spectrum of differences. The group sample size will also be different for each procedure, depending not only on how many Lisinopril subjects are involved, but also on how many subjects were used to establish the mean for "normals". Thus, the curves represent a lower bound for power when the smaller of the two groups contains n subjects. The Type I error rate for these calculations was set at 5%. In terms of power, Figure 3 shows, for example that if the mean difference between Lisinopril subjects and "normal" subjects is one-half of a standard deviation, then the probability that the t-test will be statistically significant at the .05 level when n = 50 is about .70.

h. Data storage: Data will be recorded and maintained on the VAX6020 located within AL/AOC. This hardware hosts the Rdb™ relational database software. This software provides advanced data security as part of its design features, and hosts all of our current archived evaluee data. Record access can be restricted to particular users, so that identifiable data on any study participant cannot be obtained by unauthorized users or released without the individual's express written consent. Any data recorded using desktop, laptop, notebook or other computers will be recorded directly onto appropriate mini floppy diskettes without backup to the computer's resident hard disk. Microcomputer data files will be labeled using the first four letters of the subject's last name (or underscore to indicate blanks in the event that the last name has fewer than four letters) and the last four numbers of the subject's social security account number. The extension will indicate the test recorded in that file. The diskettes will be removed from the computer only by the examiner and placed in a locked container until they can be uploaded to Rdb™. When all the data from a given floppy have been uploaded, the floppy will be reformatted to erase all usable references to the original data.

i. Safety Precautions and Measures: All medical evaluation and procedures accomplished at the Clinical Sciences Division and the Crew Technology Directorate are accomplished by personnel assigned to their respective organizations. Both organizations have Quality Assurance committees which review professional personnel qualifications and procedural compliance to appropriate regulatory directives. The medical data that will be collected for this research will be extracted from medical records with the explicit written permission of the individuals evaluated.

11. **Medical Risk Analysis**:

a. Information briefed to subjects.

1) All subjects will be briefed on the nature, purpose and goals of this research project and will acknowledge by signing the Lisinopril Study consent form (attachment 1).

2) Medical evaluation procedures accomplished as part of the subjects' aeromedical evaluation that pose any potential medical risks will be briefed prior to the accomplishment of that procedure, and a signed consent form will be placed in the ACS medical record. These procedures include exercise treadmill on all evaluees and centrifuge testing on high performance aviators.

b. Benefit vs. risk:

1) Individual study participants accept no additional personal or medical risk by consenting to inclusion into this study. No additional testing to the existing aeromedical occupational ACS evaluation is required.

2) The benefit for the individual study participant is that the possibility exists that, after the results of the study are presented to the USAF/SG, a policy requiring less comprehensive examination for hypertension in aviators treated with lisinopril will be directed. Additionally, if any medical condition is detected during the course of their evaluation, the subjects will be informed of the

medical findings and appropriate medical care for the previously undiscovered condition will be recommended.

Attachments:
1. Voluntary Consent 'The Evaluation of Medical Waiver
Requirements for the Use of Lisinopril in USAF Aircrew' **(NOT INCLUDED IN INTERIM REPORT)**
2. Armstrong Laboratory Clinical Sciences Division 'Aeromedical
Evaluation for Aircrew on Lisinopril for Hypertension' with attachments

REFERENCES

1. Bailar JC, Mosteller F, eds. Medical uses of statistics, 2nd ed. Boston: NEJM, 1992.

2. Barnes JM, Barnes NM, Costall B, Coughlan J, Kelly ME, Naylor RJ, Tomkins DM, Williams TJ. Angiotensin-converting enzyme inhibition, angiotensin, and congition. J. Cardiovasc. Pharmacol. 1992;19:S63-71.

3. Barnes, JM, Barnes NM, Costall B, Horovitz ZP, Ironside JW, Naylor RJ, Williams TJ. Angiotensin II inhibits cortical cholinergic function: implications for cognition. J. Cardiovasc Pharmacol. 1990;
16(2):234-8.

4. Bulpitt CJ, Fletcher AE. Cognitive function and angiotensin-converting enzyme inhibitors in comparison with other antihypertensive drugs. J. Cardiovasc. Pharmacol. 1992;19:S100-4.

5. Cameron HA, Higgins TJ. Clinical experience with lisinopril; observations on safety and tolerability. J. Hum. Hypertens. 1989;3:177-86.

6. Cinotti GA, Bossini A, Cagli V, Corea L, DiVeroli C, Morabito S, Pierucci A, Porcellati C, Savino K, Timio M. Multicenter clinical study of the antihypertensive activity of lisinopril. Minerva Med. 1989;80(1):53-63.

7. Espinel CH, Williams JL, Coughlin SS. Enalapril and lisinorpril in the treatment of mild to moderate essential hypertension. Clin Ther. 1990;12(2):181-90.

8. Feman SS, Mericle RA, Reed GW, May JM, Workman RJ. Serum angiotensin converting enzyme in diabetic patients. Am. J. Med. Sci. 1993;305(5):280-4.

9. Frimodt-Moeller J, Poulsen DL, Kornerup HJ, Bech P. Quality of life, side effects, and efficacy of lisinopril compared with metoprolol in patients with mild to moderate essential hypertension. J. Hum. Hypertens. 1991;5(3):215-21.

10. Genest JJ, McNamara JR, Salem DN, Schaefer EJ. Prevalence of risk factors in men with premature coronary artery disease. Am. J. Cardiol. 1991;67(15):1185-9.

11. Gilbert BW. Ace inhibitors and regression of left ventricular hypertrophy. Clin. Cardiol. 1992;15(10):711-4.

12. Gillingham KK, Fosdick JP. High-G training for fighter aircrew. Aviat. Space Environ. Med. 1988;59:12-9.

13. Gillingham KK, Schade CM, Jackson WG, Gilstrap LC. Women's G tolerance. Aviat. Space Environ. Med. 1986;57:745-53.

14. Gillingham KK. G-tolerance standards for aircrew training and selection. Aviat. Space Environ. Med. 1987;58:1024-6.

15. Herpin D, Conte D. Assessment of the antihypertensive effect of lisinopril using 24-hour ambulatory monitoring. J. Hum. Hypertens. 1989;3:11-15.

16. Hull DH, Wolthuis RA, Gillingham KK, Triebwasser JH. Relaxed +Gz tolerance in healthy men: effect of age. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 1978;45(4):626-29.

17. Israili ZH, Hall WD. Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy: a review of the literature and pathophysiology. Ann. Intern. Med. 1992;117(3):234-42.

18. Jackson WE, Holmes DL, Garg SK, Harris S, Chase HP. Angiotensin-converting enzyme inhibitor therapy and diabetic retinopathy. Ann. Ophthalmol. 1992;24(3):99-103.

19. Jain M, Armstrong L, Hall J. Predisposition to and late onset of upper airway obstruction following angiotensin-converting enzyme inhibitor therapy. Chest. 1992;102(3):871-4.

20. Karlberg BE, Rosenqvist U. Antihypertensive and hormonal effects of lisinopril, a new angiotensin converting enzyme (ACE) inhibitor in patients with renovascular hypertension. Acta. Med. Scand. Suppl. 1986;714:33-42.

21. Kochar MS, Bolek G, Kalbfleisch JH, Olzinski P. A 52-week comparison of lisinopril, hydrochlorothiazide, and their combination in hypertension. J. Clin. Pharmacol. 1987;27(5):373-7.

22. Mehta J, Lopez LM, Thorman AD. Lisinopril versus lisinopril plus hydrochlorothiazide in essential hypertension. Am. J. Cardiol. 1988;61(10):803-6.

23. Milavetz JJ, Popovtzer MM. Angiotensin-converting enzyme inhibitors and glycosuria. Arch. Intern. Med. 1992;152(5):1081-3.

24. Morlin C, Baglivo H, Boeijinga JK, Breckenridge AM, Clement D, Johnston GD, Klein W, Kramer R, Luccioni R, Meurer KA. Comparative trial of lisinopril and nifedipine in mild to severe essential hypertension. J. Cardiovasc. Pharmacol. 1987;9:S49-52.

25. Moyses C, Higgins TJ. Safety of long-term use of lisinopril for congestive heart failure. Am. J. Cardiol. 1992;70(10):91C-97C.

26. Murray NH. Duration of angiotensin-converting enzyme inhibition: implication for tolerability. Cardiology. 1991;79:22-9.

27. Paul MA, Gray GW. The effect of captopril on +Gz tolerance of normotensives. Aviat. Space Environ. Med. 1992;63:706-8.

28. Simons LA. Triglyceride levels and the risk of coronary artery disease: a view from Australia. Am. J. Cardiol. 1992;70(19):14H-18H.

29. Swedish Lisinopril Study Group. Lisinopril combined with atenolol in the treatment of hypertension. J. Cardiovasc. Pharmacol. 1991;18(3):457-61.

30. Thind GS. Angiotensin converting enzyme inhibitors: comparative structure, pharmacokinetics, and pharmacodynamics. Cardiovasc. Drugs Ther. 1990;4(1):199-206.

31. Tuomilehto J, Wikstrand J, Warnold I, Olsson G, Elmfeldt D, Berglund G. Coronary Artery Disease can be prevented by antihypertensive therapy: experiences from the MAPHY Study. J. Cardiovasc. Pharmacol. 1990;16:S75-6.

32. Webb JT, Oakley CJ, Meeker LJ. Unpredictability of fighter pilot G tolerance using anthropometric and physiologic variables. Aviat. Space Environ. Med. 1991;62(2):128-35.

33. Whelton A. Application of ambulatory blood pressure monitoring to clinical therapeutic decisions in hypertension. J. Hypertens. Suppl. 1991;9(1):S21-5.

34. Whinnery JE. Medical considerations for human exposure to acceleration-induced loss of consciousness. Aviat. Space Environ. Med. 1991;62(7):618-23.

35. Whinnery JE. Acceleration tolerance of asymptomatic aircrew with mitral valve prolapse. Aviat. Space Environ. Med. 1986;57:986-92.

36. Zemel PC, Sowers JR. Relation between lipids and atherosclerosis: epidemiologic evidence and clinical implications. Am. J. Cardiol. 1990;66(21):71-121.

Hypertension

A1.7. Aeromedical Concerns. Hypertension is associated with cardiovascular events carrying a significant incidence of sudden incapacity or death. The level of the blood pressure is related to the level of risk.

A1.8. Waiver. Unrestricted waiver is possible if adequate control of blood pressure is achieved (BP<140/90) and absence of end-organ damage is confirmed. The use of Lisinopril may be compatible with unrestricted waiver provided patients pass ENT evaluation, psychometric testing and centrifuge assessments at Brooks AFB. Hypertension controlled by diet and exercise alone does require waiver although a mild hypertensive (BP<150/100) may continue on flying status without a waiver request being submitted for the first 6 months only while diet and exercise control of blood pressure is attempted.

A1.9. Information Required. Internal medicine consultation is normally required. However, if the patient is on Lisinopril an evaluation following a standard protocol is required at Brooks AFB. Renewal requests should include results of blood urea, electrolytes, uric acid and also quarterly blood pressure measurements.

A1.10. Treatment. Hydrochlorothiazide (HCT)/triamterine, with or without potassium supplements, is compatible with waiver. Appropriate surgical treatment of secondary hypertension is also allowed. At present, Lisinopril is permitted without assessment at Brooks AFB only in Class III aviators. All other forms of treatment are disqualifying.

A1.11. Discussion. In the Framingham study, the mortality of hypertensives was more than double that of the normotensive populations, with most of the deaths occurring suddenly. Theä risk of cardiovascular events is heightened by age, smoking, gender, family history, excess alcohol intake and high blood lipid levels; the presence of one or more of these risk factors may contribute to the final aviation disposition of the case. Several studies have demonstrated a reduction in mortality and morbidity resulting from the treatment of hypertensive patients. Beta blockers may cause sedation, affect Gz tolerance and have other side effects. At least one Angiotensin Converting Enzyme (ACE) inhibitor (Captopril) has a significant effect on the relaxed and straining Gz tolerance of normotensives; the use of ACE inhibitors in hypertensive aircrew therefore necessitates caution.

A1.12. US Air Force Experience. Almost 90% of aircrew with hypertension have received waivers, the exact category of which has depended on the therapeutic agent used.

24 Mar 97

MEMORANDUM FOR LT COL COURTNEY SCOTT
HQ AFMOA/SGPA
170 Luke Ave., Ste. 400
Bolling AFB, DC 20332-5113

FROM: AL/AOCI
2507 Kennedy Circle
Brooks AFB, TX 78235-5117

SUBJECT: Coronary Primary Prevention Program

1. Although the National Institutes of Health published its National Cholesterol Education Program (NCEP) guidelines in 1988, followed by a second report in 1993[1], lowering lipids by pharmacologic means had not, until recently, been shown to reduce total mortality in patients without known atherosclerosis (primary prevention). Drug therapy with resin-binders[2,3] and gemfibrozil[4] had been shown to reduce the incidence of myocardial infarction in primary prevention studies, but an increase in noncardiovascular deaths negated the overall benefit on all-cause mortality in those studies. Whether this was chance, or an unexpected effect of medication or even of lipid lowering, is not clear. However, probably the most likely explanation for the failure to affect overall mortality lies in the fact that because these were short term studies with modestly effective drugs, the impact on coronary mortality was not striking enough to overcome the inherent "noise" to which all-cause mortality is prone. More recently, the West of Scotland Coronary Prevention Study Group (WOS), using a statin for primary prevention, demonstrated a 32% reduction in death from cardiovascular causes, and a 22% reduction in all-cause mortality[5]. While the five year duration of follow-up was similar to earlier studies, HMG CoA reductase inhibitors are profoundly effective at reducing lipid levels, with a 20% reduction in total cholesterol and a 26% reduction in LDL cholesterol in the preceding study. Not surprisingly, HMG CoA reductase inhibitors have also shown a highly significant effect in secondary prevention, i.e., prevention of disease progression in patients with known atherosclerosis. In the Scandinavian Simvastatin Survival Study Group (4S) trial, simvastatin resulted in reductions of total cholesterol and LDL cholesterol of 25% and 35%, respectively, compared to placebo. The treated group showed a 42% reduction in coronary deaths, and a 30% reduction in all-cause mortality.[6] Neither WOS nor 4S showed any increase in noncardiovascular mortality in the treatment groups. The initial controversy over the guidelines espoused by the NCEP has largely subsided. Oliver illustrated this shift in a recent article, stating "My article of more than three years ago suggested that the NCEP endorsement of serum cholesterol reduction as a means of preventing CAD was stronger than the facts warranted. However, evidence subsequently furnished by several seminal clinical trials have supported most of the NCEP conclusions. My earlier reservations are mostly superseded, and we can now state with confidence that reduction of elevated blood cholesterol levels does lead to less CHD."[7]

2. NCEP guidelines were used as the basis for the following recommendations for coronary primary prevention in aviators, but were adapted in several areas as follows:

a. The NCEP panel recommended considering drug therapy after age 35 in men, and after menopause in women; they considered age greater than or equal to 45 in men, and age greater than or equal to 55 in women, to be positive risk factors for coronary disease. As an alternative, the Aeromedical Consult Service (ACS) suggests using ages 40 and 50 in men and women respectively for intervention and screening thresholds, because our review of cardiac events in USAF aviators found the risk, at least for males, showed a striking increase in the 45-49 year age group.[8] From prevention studies, about five years of pharmacotherapy seems to be required to exert an effect. Since age 40 is a threshold age for other portions of the physical exam, it also simplifies this program.

b. The initial portion of the NCEP recommendations addresses who should be screened with serum lipid testing, with cost effectiveness as a major issue. Cost was indeed an issue, since these guidelines were meant to apply to the entire United States population. Clearly, in a small group of military aviators engaged in a high risk, expensive occupation, obtaining HDL and triglyceride levels in addition to total cholesterol is a minimal cost issue.

c. Certain risk factors such as clinical diabetes are, for obvious reasons, not considered.

d. NCEP guidelines do not consider noninvasive screening for coronary disease, since in the general population it is not indicated. There are no data to show any benefit to therapeutic intervention in most asymptomatic coronary disease; in essence, since nothing would be done with the answer, the question need not be raised. On the other hand, the finding of asymptomatic coronary disease in the military aviator is clearly of significance, and requires occupational intervention.

3. At present a fasting lipid panel is obtained at each long physical; with the projected disappearance of the long physical, the interval for future testing has yet to be decided. (Even for the general U.S. population, NCEP guidelines recommended cholesterol determination at least once every five years beginning at the age of 20.) At any age, a Step I diet should be recommended for LDL greater than or equal to 130 mg/dl. A Step 1 diet involves an intake of saturated fat constituting 8-10% of total calories, and less than 300 mg of cholesterol per day. At the first physical exam upon reaching age 40, an LDL greater than or equal to 190 mg/dl, or an LDL greater than or equal to 160 mg/dl together with one or more risk factors, should prompt a repeat fasting lipid panel for confirmation. (Risk factors consist of (a) family history of coronary heart disease with a coronary event earlier than age 55 in a first degree male relative or earlier than age 65 in a first degree female relative, (b) current smoking, (c) hypertension, treated or not, and (d) low HDL cholesterol of less than 35 mg/dl. High HDL, defined as greater than or equal to 60 mg/dl, is considered a negative risk factor and should be subtracted from any sum of positive risk factors.) If the repeat lipid study yields an average LDL greater than or equal to 190 mg/dl, or 160 mg/dl with one or more risk factors, the flight surgeon should prescribe a Step II diet, with saturated fat less than 7% of total calories, and less than 200 milligrams per day of cholesterol. Lipid panels should be repeated at three months for reinforcement, and at six months for reassessment. If LDL is not under threshold values at six months, pharmacologic therapy should be begun with lovastatin, resin-binders, or combination therapy, all acceptable for unrestricted Flying Class II waiver after a ground trial. Gemfibrozil, considered a minor hypolipidemic agent, is waiverable for Flying Class IIA duties alone or in combination with resin-binders. Combination therapy with gemfibrozil and lovastatin is not waiverable due to an unacceptable incidence of myopathy. Lipid values should be repeated again at three and six months, with a preferred target of 160 mg/dl, or 130 mg/dl with risk factors. Continued elevation of the LDL suggests either difficulties with compliance or a resistant problem. In either case, the aviator whose LDL after six months of therapy remains above 190 mg/dl, or 160 mg/dl with risk

factors, should be evaluated with an exercise tolerance test and coronary fluoroscopy, with the results sent to the ACS.

4. A screening program per se is designed to detect disease, usually at significant cost, and without necessarily providing treatment guidelines. This program, on the other hand, is designed to provide practice guidelines while following recommendations already in place for the general public, and to screen only those who fail to respond. To estimate the number likely to be affected, we reviewed 376 ACS evaluees referred for aortic insufficiency or mitral valve prolapse over the last ten years. These diagnoses were chosen because lipid panels were available in each case, and because there is no known association between atherosclerosis and either diagnosis, which should preclude a confounding effect. Of these 376 evaluees, subjects were excluded for study if they were not USAF aviators in Flying Class II status between the ages of 40-55, which left 267 evaluees for analysis. Two hundred twenty-five of 267 (84%) had an LDL less than 160 mg/dl. Thirty-one of 267 (12%) had an LDL greater than or equal to 160 mg/dl, but less than 190 mg/dl; of these, only eight (3%) had an additional risk factor. Eleven of 167 (4%) had an LDL greater than or equal to 190 mg/dl. Thus, 7% would have been candidates for aggressive dietary therapy, and possibly pharmacotherapy. With the efficacy of drug, especially statin, therapy, the number requiring screening after failure of pharmacotherapy would have been expected to be very small. The EXCEL Study found that, depending on lovastatin dose, 80-96% of patients reached an LDL target of less than 160 mg/dl.[9] Thus, we would project that fewer than 1% of aviators over age 40 would actually proceed to any screening studies.

JEB S. PICKARD, Col, USAF, MC, FS
Chief, Internal Medicine Branch

REFERENCES

1. Summary of the second report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel II). JAMA 1993;269:3015-23.

2. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. JAMA 1984;251:351-64.

3. The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. JAMA 1984;251:365-74.

4. Frick MH, Elo O, Haapa K, et al. Helsinki heart study: primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia: safety of treatment, changes in risk factors, and incidence of coronary heart disease. N Engl J Med 1987;317:1237-45.

5. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med 1995;333:1301-7.

6. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383-9.

7. Oliver MF. Revisitation. Lowering cholesterol for primary prevention of coronary heart disease: extrapolation beyond the facts? ACC Current Journal Review 1996;5(3):9-11.

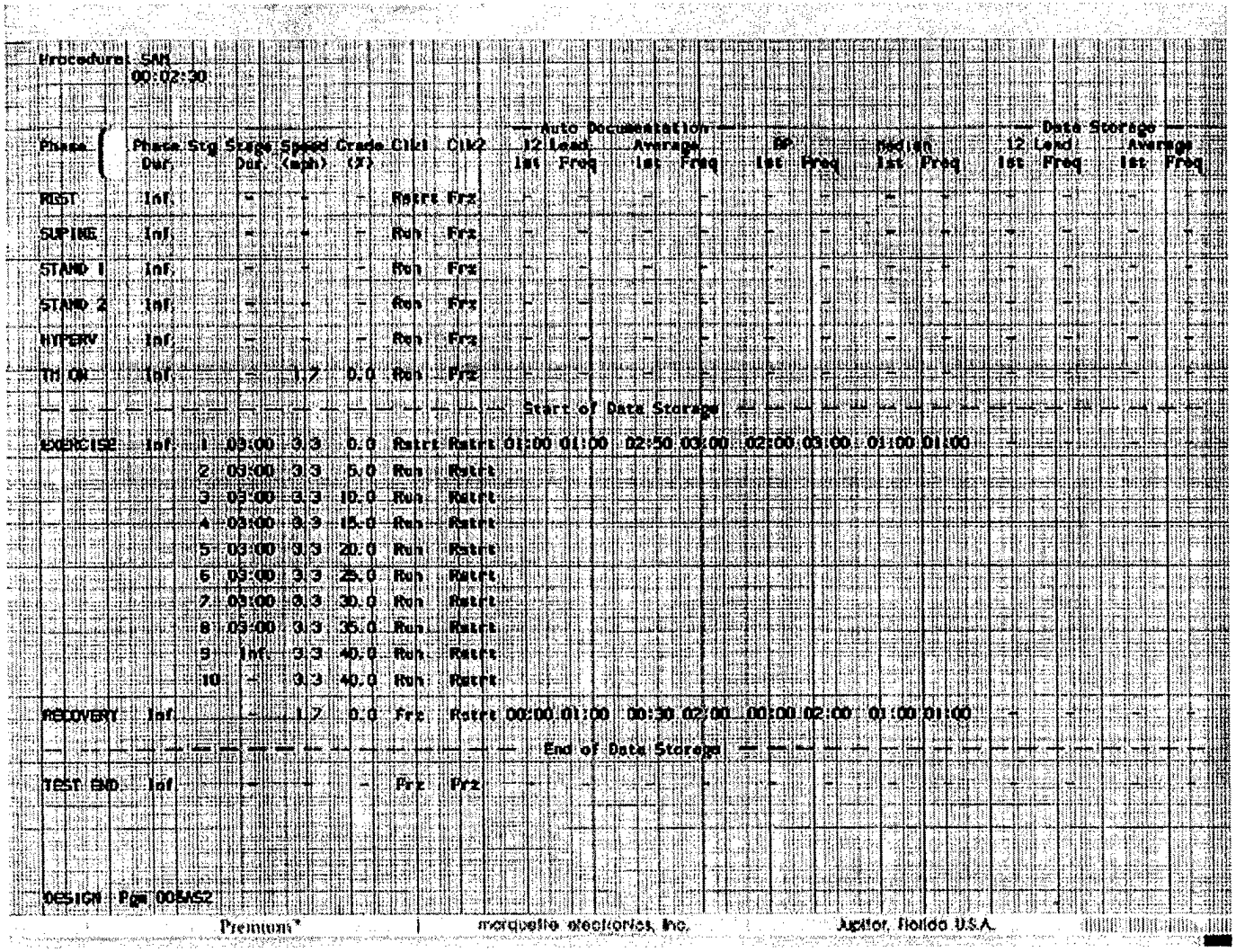
8. Osswald SS, Miles R, Nixon W, Celio P. Review of cardiac events in USAF aviators. Aviat Space Environ Med 1996;67:1023-7.

9. Bradford RH, Shear CL, Chremos AN, et al. Expanded Clinical Evaluation of Lovastatin (EXCEL) Study results. I. Efficacy in modifying plasma lipoproteins and adverse event profile in 8245 patients with moderate hypercholesterolemia. Arch Int Med 1991;151:43-9.

Modified Balke Protocol

Wolthuis R, Froelicher V, Fischer J. A new practical clinical treadmill protocol.
Am J Cardiol 1977 May 4;39(5):697-700.

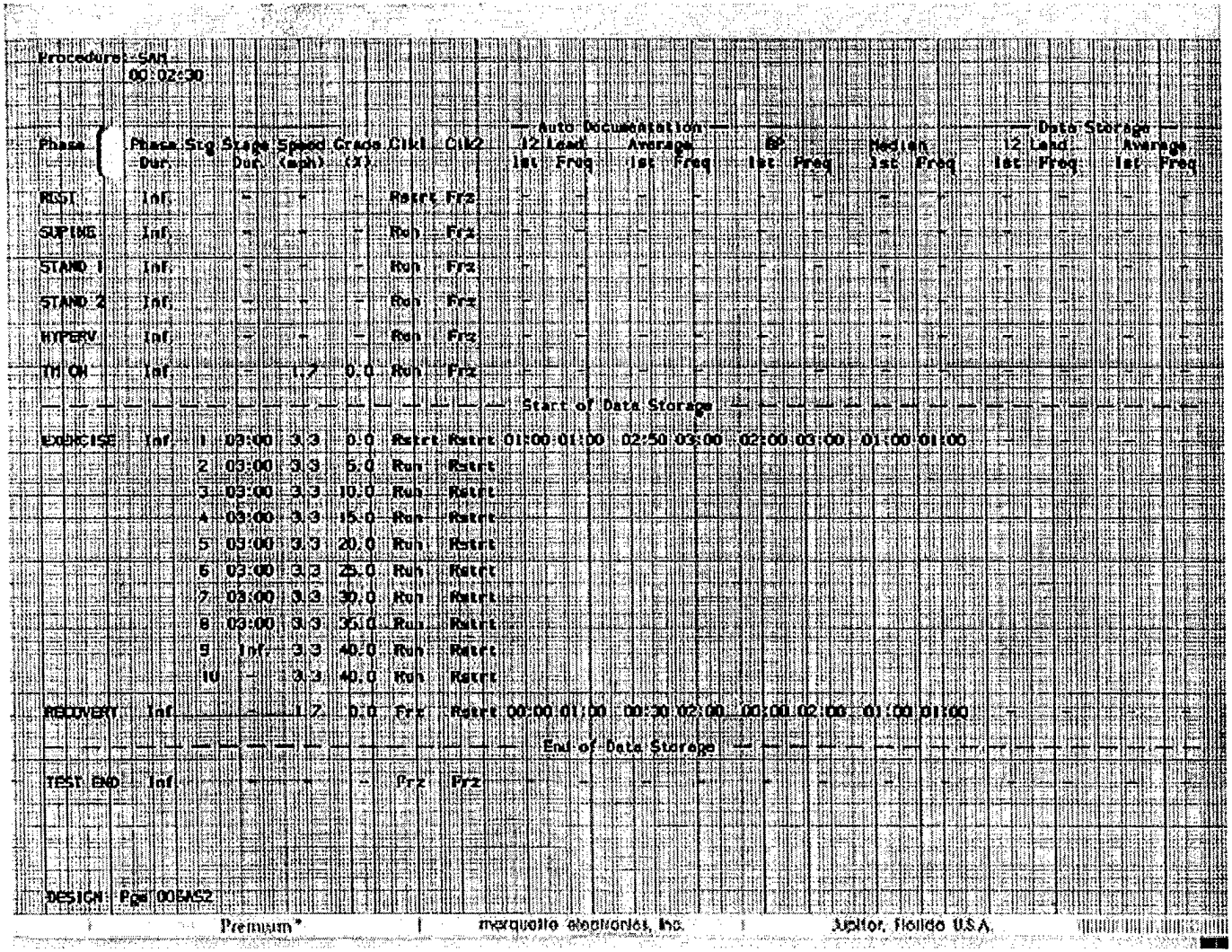
It is done at a constant speed of 3.3 mph and starts at an incline of 0% grade, increasing in grade by 5% every three minutes up to a grade of 40% which is the treadmill machine limit (and that is with special modification to the machine). - Dr. William Kruyer



Modified Balke Protocol

Wolthuis R, Froelicher V, Fischer J. A new practical clinical treadmill protocol.
Am J Cardiol 1977 May 4;39(5):697-700.

It is done at a constant speed of 3.3 mph and starts at an incline of 0% grade, increasing in grade by 5% every three minutes up to a grade of 40% which is the treadmill machine limit (and that is with special modification to the machine). - Dr. William Kruyer



GUIDELINES FOR COMPLETING AEROMEDICAL SUMMARIES

Section I: Introduction
(Patient Identification / Duty Information / Purpose of Submission)

As a minimum, the following information should be included in the introductory paragraph of every Aeromedical Summary:

- Name, Rank, and SSAN of the patient.
- Organization, MAJCOM, and current base of assignment
- Crew position, ASC, type of aircraft, number of hours logged, and DAFSC.
- Purpose of this submission. What are you asking us to do.
- A typical opening to the summary might read:
  "A physical exam was recently completed on Colonel Johnny Jet who holds a Flying Class IIC waiver for mitral valve prolapse (MVP), granted initially on 14 December 1988 by HQ USAF/SGPA, most recently renewed on 31 December 1993 by HQ ACC/SGPA, and which expires on 31 December 1996."

  Col Jet, 012-34-5678, is a 42-year-old, active duty, command pilot in the T-38, (ASC: 3A; DAFSC: 18A5) with 22 years of active service and a total of 3500 flying hours (800 civilian, B-737), 50 of which have been logged in the past six months. He is currently the Operations Group Commander for the 12th FTW, Randolph AFB, TX. Reevaluation at the Aeromedical Consultation Service is now required in accordance with the Surgeon Generals' MVP Management group, as specified on his last waiver.

- Include any additional information you think we should be aware of, i.e., pending PCS, change in assigned aircraft, etc...
- Specify the date of the most recent DNIF recommendation, if appropriate.

Section II: History (Significant Medical History)

- Describe in detail the circumstances surrounding the discovery and evaluation of the current medical issue (if this is a re-eval, a more concise description may be sufficient).
- In any AMS requesting waiver for a new condition, include names and phone numbers of witnesses, EMS personnel, or hospital ERs, if any were involved.
- Include previous surgeries and any other significant medical problems.
- List previous / current waivers, the diagnosis, date of initial and current waiver, waiver authority, and date of the current waivers' expiration.

Section III: Physical (Current Physical Examination Results and Objective Data)

- Include the results of any specialty consultations obtained.
- Describe your hands on physical examination of the patient, being certain your examination is thorough enough to adequately evaluate the problem being addressed.
- Include results of diagnostic studies to include local normal lab values.
- Review AFPAM 48-132, Medical Waivers for Aircrew, to ensure all requirements have been addressed. The ACC/SGPA Tactics Book is another valuable resource for many medical conditions.

SECTION IV: Diagnoses

- List all aeromedically significant diagnoses.
- List any clinically interesting findings.
- Identify any permanent/indefinite waivers held.
- Specify those diagnoses requiring waiver or re-waiver at this time.

SECTION V: Recommendations

- What do you want us to do? Waiver? DQ? Make a recommendation and justify it.
- Justification! Why should a waiver be granted? What can / can't the examinee do? Impact on individual health, flight safety, mission accomplishment?
- Refer to AFI 48-123 chapter 7, section 5.1 or AFPAM 48-132 section 6, Introduction and Waiver Criteria, for the general criteria a medical condition must meet in order to be considered "waiverable."
- Including a squadron or wing commanders' recommendation can be of great benefit in cases where a period of observation for diagnoses in which performance related issues are of concern.
- References to current medical literature in support of your recommendation are extremely helpful, particularly in controversial or potentially precedent setting cases.

MEMORANDUM FOR USAFSAM/AFCF

FROM: TSgt JOE JET (P.O.C.) <POINT OF CONTACT>
3RD AMDS/SGPF <COMPLETE MTF ADDRESS>
BLDG. 24-850 HOSPITAL DRIVE
ELMENDORF AFB AK
99506-3700
DSN 317-552-1363/3433 <ACCURATE PHONE #>
FAX DSN 317-552-8483 <ACCURATE FAX #>

SUBJECT:INITIAL EVAL/RE-EVAL/ FOR ACS APPOINTMENT ON.....
REVIEW ONLY BY ACS STAFF <WHY ARE YOU SENDING THIS?>

1. Attached is the AMS and additional studies on -

SUBJECT NAME: <CAN BE DONE IN PEN>
SSAN:
DATE OF BIRTH:
DEROS: <IF APPLICABLE>
CREW POSITION:
ASC:
DATE OF DNIF: <IF APPLICABLE>
DATE OF LAST EXAM:
SUBJECTS COMMAND OF ASSIGNMENT: < MAY BE DIFFERENT THAN MTF"S>
DIAGNOSIS:

DATES OF PREFERENCE FOR SCHEDULING: <IF ASAP , **YOU NEED TO EXPLAIN**>
DATES SCHEDULING CANNOT BE ACCOMPLISHED: <i.e. TDY, LEAVE, EXERCISE>
ADDITIONAL COMMENTS:

SIGNATURE OF P.O.C.
NCOIC, FLIGHT MEDICINE/PES

BY ORDER OF THE
SECRETARY OF THE AIR FORCE

AIR FORCE INSTRUCTION 11-404
22 JULY 1994

Flying Operations

CENTRIFUGE TRAINING FOR HIGH-G AIRCREW

This instruction implements AFPD 11-4, *Flying Operations, Aviation Service.* It provides guidance and procedures for the Centrifuge Training of aircrew who are either currently flying or are selected to fly high-G aircraft (HGA). It describes the initial and refresher centrifuge training requirements, as well as guidance and procedures for the handling of aircrew who do not satisfactorily complete this training program. AFI 11-403, *Air Force Aerospace Physiological Training Program,* complements this instruction by providing detail on the training requirements for aerospace physiologists and centrifuge technicians. AFPAM 11-404, *G-Awareness for Aircrew,* provides comprehensive information on the physiology of G-awareness.

SUMMARY OF CHANGES

This revision updates centrifuge training procedures for high-G aircrew.

OPR: HQ ACC/DOTF (Maj Peter Van Lieshout)
Certified by: HQ USAF/XOO (Col R. T. Newell III)

Pages: 8/Distribution: F

Chapter 1

INTRODUCTION

1.1 Purpose and Need for Centrifuge Training. The high-G aircraft operated by today's aircrew are easily capable of causing G-induced loss of consciousness (GLOC). Optimum physical conditioning, appropriate functioning of anti-G equipment, and adequate G-oriented situational awareness are all important to aircrew G-tolerance; however, an effective anti-G straining maneuver (AGSM) is the aircrew's most significant weapon against the potentially incapacitating effects of G, adding an average of 3.2 (+) G to aircrew resting G-tolerance. Centrifuge training has proven to be our best device for teaching the proper AGSM, as well as providing the opportunity for teaching the physiology of high-G flight and an awareness of the factors that affect an aircrew's G-tolerance from day to day.

1.1.1. Centrifuge training consists of initial and refresher training. Initial training is conducted during specialized undergraduate pilot training (SUPT). Initial training is also conducted "as required" for HGA aircrews who did not previously complete this training. In addition to initial training, all HGA aircrews who are either returning from 3-plus years non-flying or who are converting from a non-high G-onset rate aircraft to a high G-onset rate aircraft require refresher training.

1.1.2. There is a 12-hour, automatic duty-not-involving-flying (DNIF) following any centrifuge training.

1.1.3. The purpose of centrifuge training is to enhance combat capability and safety through the following methods:

- Increasing aircrew awareness of the potentially incapacitating effects of G-induced loss of consciousness.
- Optimizing aircrew defense against GLOC.
- Improving the aviator's tolerance to the fatiguing effects of sustained high-G operations.
- Improving aircrew performance under G-stress.
- Identifying aircrew with low G-tolerance before they enter a high-G aircraft conversion program.

1.2. Formal Training Prerequisite. Attendance of the appropriate centrifuge training program is a prerequisite for entry into all post-SUPT high-G aircraft formal training unit (FTU) courses except F-16 course F16CONXOAL, Navy Transition Training Course, and F-16 course F16BOOFS (TOP KNIFE) for non-fighter assigned flight surgeons. Foreign aircrews returning to their home country following formal training are exempt from this requirement. For aircrews who attended, but could not complete centrifuge training prior to their FTU course entry date, the FTU commander will take the following actions:

1.2.1. Follow the guidance of chapter 2 or 3 (as appropriate).

1.2.2. Determine whether the aircrew should:

- •Enter the FTU without restriction (recommended for experienced rated officers, paragraph 1.3.5.).
- •Complete the low-G or dual-only parts of the formal training course.
- •Remain at the FTU without flying until successful completion of retraining.
- •Return to losing unit for later resumption of flying training once centrifuge retraining is completed.

1.2.3. Notify Air Combat Command (ACC)/DOT of action taken and disposition of aircrew.

1.2.4. Regardless of this decision, aircrew must return for centrifuge retraining within 60-180 days of first failure or before completing unit mission qualification training. Centrifuge training must be successfully completed or a waiver approved prior to mission-ready certification.

1.3. Explanation of Terms and Abbreviations:

1.3.1. **G-Defense Training.** A comprehensive program to ensure optimum G-defense training of HGA aircrew. It consists of physiological and operational training on G-awareness and G-defense, centrifuge training, and an ongoing continuation training program. This instruction addresses only the centrifuge training program. For information regarding the physiological aspects of high-G operations, see AFPAM 11-404. For information regarding continuation training requirements, see the appropriate MCR 51-50 (or equivalent). For information regarding operational procedures or restrictions, see the appropriate MCR 55-XX (or equivalent).

1.3.2. **Active High-G Aircrew.** Any pilot, weapons system officer, electronic warfare officer, flight surgeon, or other aircrew assigned to an active flying billet (includes Air National Guard and US Air Force Reserve (USAFR) part-time aircrews) in a high-G aircraft. The provisions of this instruction apply to all active high-G aircrews, except for Companion Trainer Program (CTP) aircrews who would not otherwise require centrifuge training.

1.3.3. **Anti-G Straining Maneuver (AGSM).** The L-1 maneuver, to include muscle tensing and straining against a closed glottis in 3-second cycles.

1.3.4. **Authorized Centrifuge Training Facilities:** (as of 1 October 1993)

- Aerospace Physiological Unit, Holloman AFB, New Mexico
- RNLAF Unit, Soesterberg AB, Netherlands
- Warminster Navy Centrifuge (ANG and USAFR only, others with HQ ACC/SGP approval).

1.3.5. **High-G Aircraft (HGA).** Aircraft capable of generating a G-loading in excess of 4.0. This definition is further divided into the following two categories:
1.3.5.1. High G-Onset Rate (HGOR). Capable of rapid G-onset rates and sustained G-loading of greater than 6.0. Current USAF aircraft which meet this definition are the A-7, A/OA-10, AT-38, RF/F-4E/G, F-5, F-15, F-15E, F-16, F-22, T-38, and X-29.
1.3.5.2. Low G-Onset Rate (LGOR). All other HGA that do not meet the HGOR definition.
1.3.6. **Profiles.** A profile is one run on the centrifuge device from start (idle) to stop (return to idle or stop). Gradual onset rate is 1/10th G per second and rapid onset rate is up to 6 Gs per second.
1.3.7. **AF Form 702, Individual Physiological Training Record.** This form tracks all physiological and centrifuge training, and is normally maintained within the aircrew's flight records.
1.3.8. **Experienced Rated Officer.** For the purposes of this instruction only, an experienced rated officer is defined as a rated officer who:

- Is 40 years of age or older or is an O-7 select or higher, or
- Has logged greater than 1,000 hours in high G-onset rate aircraft.

1.4. Scheduling *(Holloman AFB unit only).* The 49th Medical Group/MGT, Holloman AFB, New Mexico, schedules all centrifuge training for their facility. The 49th Medical Group will publish and distribute a quarterly schedule to all HGA major commands (MAJCOM), numbered Air Forces (NAF), Air National Guard Reserve Center (ANGRC)/DO, and the Air Force Military Personnel Center (AFMPC)/DPMRO. Training quotas are filled on a "first-come, first-served" basis. Contact the 49th Medical Group directly at data switching newwork (DSN) 867-5771/5760 to reserve slots.

1.5. Changes. Forward recommendations for changes to the MAJCOM office of primary responsibility (OPR) or ANGRC/DO on an AF Form 847, **Recommendation for Change of Publication (Flight Publication).** The ACC/DO will staff and coordinate all changes to this instruction. The MAJCOM/DO/XO is the approval authority for changes to the MAJCOM supplemental instruction.

1.6. Supplements. See chapter 5.

1.7. Waivers. Waivers to this instruction are not authorized beyond those discussed within chapters 2 and 3 of this instruction. **EXCEPTION:** The MAJCOM/DO/XO or a delegated authority may waive the formal training prerequisite aspect of this instruction as described in paragraph 1.2. A formal training prerequisite waiver does not waive the requirement to complete centrifuge training prior to certification as mission-ready. This simply allows an aircrew to enter his or her formal training course pending attendance of centrifuge training.

Chapter 2

INITIAL TRAINING

2.1. Overview. Initial training is a one-time requirement for all active HGA aircrews, except that experienced rated officers (as defined in this instruction) will be trained to the refresher level described in chapter 3. Aircrews who fail their first attempt at initial training will attend the retraining program between 60-180 days from first failure. All training is conducted at an authorized centrifuge training facility and consists of both academic instruction and profiles. Training at Brooks AFB, Texas, requires prior HQ ACC/SGP approval

2.2 Requirements. Completion of all training prescribed by this section is required; except, in event of equipment malfunction, training may be completed without profiles 4 or 5. Only a qualified aerospace physiologist (reference AFI 11-403) is authorized to document centrifuge training completion on the AF Form 702. Documentation will reflect "AFI 11-404 initial centrifuge training complete." Training consists of the following:

2.2.1. **Platform Academic Instruction.** Minimum 2 hours of platform academic instruction covering the effects of acceleration forces on mobility and respiration, characteristics of GLOC, techniques of an effective AGSM, and protection offered by current and future anti-G systems. Also, included will be an interactive discussion of the impact of physical conditioning, lifestyle, and proper nutrition on individual G-tolerance and on the effectiveness of the AGSM. "There I was" discussions are encouraged.
2.2.2. **Five Centrifuge Profiles.** Aircrews currently flying or converting to the F-16 (or any future aircraft with a reclined seat) will train in the 30-degree reclined seat. All other aircrews will train in the 13-degree straight-up seat. The maximum G identified in each profile will be adjusted as noted for the reclined seat. All profiles will be videotaped. The following are the training profiles and will be accomplished in the order listed:
2.2.2.1. First profile. Gradual onset run to second peripheral light loss (after initiation of AGSM) or 8 Gs (9

Gs reclined seat), whichever occurs first. The purpose of this run is to determine the aircrew's resting G-tolerance (established by first peripheral light loss while relaxed or prior to initiation of AGSM) and then to determine the effectiveness of the AGSM. The G-suit is not functional for this run.

2.2.2.2. Second profile. Rapid onset run to 1 G above resting tolerance or 7 Gs (whichever occurs first) for 30 seconds. The purpose of this run is to practice the proper AGSM. The G-suit is connected for this and all subsequent runs.

2.2.2.3. Third profile. Rapid onset run to 7.5 Gs (9 Gs reclined seat) for 15 seconds. Satisfactory completion of this profile is mandatory to complete training. If performance is not satisfactory, the aircrew may request another practice of the second profile, then reattempt the third profile.

2.2.2.4. Fourth profile. Rapid onset run to 6 Gs (7 Gs reclined) for 10 seconds during "check 6" position (looking over left shoulder) although the goal is to maintain maximum G for 10 seconds.

2.2.2.5. Fifth profile. Simulated air combat mission. The aircrew tracks a target through a series of maneuvers at a 3 Gs minimum with maximum G and onset rate tailored to the capabilities of the aircrew's gaining aircraft.

2.2.3. **Debrief.** Aircrews will receive a verbal debrief following each profile, with emphasis on improving each aircrew's AGSM. The overall debrief will include a review of the aircrew's videotape with emphasis on the AGSM and, if warranted, a written recommendation to the aircrew for a tailored conditioning program designed to increase the individual's potential G-tolerance. This recommended program will include lifestyle and physical conditioning comments as appropriate.

2.3. Noncompletion of Training. If training is incomplete due to factors beyond the aircrew's control, no action is required beyond rescheduling training. Recommendation for noncompletion due to aircrew performance is made by the aerospace physiologist who monitored the individual's training. The training facility chief is the final authority for determining noncompletion. Once this recommendation is validated, the procedures in this section will be implemented.

2.3.1. **First Attempt Failure:**

2.3.1.1. **Notification.** The centrifuge facility chief will notify the aircrew's commander in writing of the failure and provide a copy of the aircrew's training report and the tailored conditioning program recommended in the debrief. For aircrews en route to a FTU, this notification is sent to the FTU squadron commander. The centrifuge facility chief may recommend flight restrictions for pilots whose centrifuge performance indicates a significantly higher propensity for G-induced problems. MAJCOM or ANGRC notification for first time failures is not required.

2.3.1.2. **Grounding.** Aircrews are not medically grounded following their first attempt at initial training beyond the 12-hour automatic DNIF.

2.3.1.3. **Restrictions.** There is no automatic restriction following first-attempt failure. Following review of the centrifuge training record and consultation with the flight surgeon and centrifuge facility chief, the squadron commander may restrict pilot aircrews from solo high-G operations until successful completion of centrifuge retraining.

2.3.1.4. **Conditioning program.** The aircrew's commander or commander-designated representative will monitor the aircrew's progress in the conditioning program. Aircrews must be afforded sufficient opportunity (minimum three times per week) to work on their individual conditioning program. Aircrews who have weight training recommended as part of this program should seek professional assistance in establishing their program. When diet or lifestyle changes are recommended, the aircrew member should seek appropriate assistance from the unit medical group or other base agencies.

2.3.1.5. **Scheduling centrifuge retraining.** Retraining will be scheduled for 60-180 days following the aircrew's initial training. The commander and flight surgeon will review the aircrew's progress in the conditioning program prior to scheduling retraining. Aircrews are grounded on the 181st day following their first attempt until satisfactory completion of retraining or MAJCOM/DO/XO or ANGRC/DO waiver is approved.

2.3.1.6. **Retraining program.** The retraining program is only conducted at authorized centrifuge training facilities. A qualified aerospace physiologist will conduct or monitor the complete retraining program. This program is 3 days in duration and consists of the following:

- Review of videotape and training report from the first training attempt.
- Review of progress made during individual conditioning program.
- Academics tailored to the individual's original problem areas.
- Centrifuge training profiles tailored to the individual's needs. The purpose of these profiles is to work on the aircrew's specific problem areas as identified in initial training. Additional warm-up profiles will be provided as necessary (or at the request of the aircrew) to prepare the aircrew for reaccomplishment of the initial training third profile.
- Third centrifuge profile from initial training program (paragraph 2.2.2.3.). Aircrews must complete this profile to the satisfaction of the aerospace physiologist and training facility chief before the aircrew's AF Form 702 will be documented reflecting completion of initial training. This profile may be attempted on the

first or second day of retraining following a recommendation by the aerospace physiologist and with concurrence of the aircrew. Once the aircrew satisfactorily completes this profile, the AF Form 702 will be signed and no further retraining is necessary.

2.3.2. **Second Attempt Failure:** *(aircrew fails retraining program)*

2.3.2.1. **Notification.** The centrifuge facility chief will notify the aircrew's commander in writing and provide an information copy to the MAJCOM/DOT/XOT/SGP or ANGRC/DOT/SGP, and to HQ ACC/SGP, of the aircrew's failure to complete retraining. Notification must include the reasons for the failure and should include any recommendations that might be beneficial in determining the future training ability of the aircrew.

2.3.2.2. **Grounding and medical evaluation.** Aircrews are medically grounded pending completion of a medical evaluation by a qualified flight surgeon. The purpose of this evaluation is to determine if there is any underlying pathology that caused or contributed to the aircrew's failure to complete training. Results of this evaluation will be provided to the unit commander and the MAJCOM/SGP or ANGRC/SGP. Following satisfactory completion of treatment (if underlying pathology was a factor), recommendation by the attending flight surgeon, and concurrence by the MAJCOM/SGP or ANGRC/SGP, the aircrew may reattempt initial centrifuge training without prejudice. If no underlying pathology was discovered, then the remaining procedures in this section will be implemented.

2.3.2.3. **Restrictions.** Following successful completion of a medical evaluation, aircrews may, with commander approval, resume limited flying duties. Pilots will not fly solo or as pilot-in-command, instructor, or flight examiner until completion of an operational review and approval of a MAJCOM/DO/XO or ANGRC/DO waiver.

2.3.2.4. **Operational review.** The aircrew's operations group commander or equivalent will conduct a unit-level operational review. The purpose of this review is to provide a recommendation to the MAJCOM/DO/XO or ANGRC/DO as to whether the aircrew should receive a waiver to continue in their weapons system. The operations group commander must consider the aircrew's flying skill and experience, then determine the aircrew's potential to develop into a successful high-G aviator. If the aircrew is converting from a low to a high G-onset rate aircraft, or is new to HGA aviation, then the operations group commander will recommend either retaining the aircrew in a lower G system or approval to continue in HGA conversion. The operations group commander's recommendation will be sent to the MAJCOM/DO/XO or ANGRC/DO within 60 days of the aircrew's failure of retraining.

2.3.2.5. **MAJCOM/ANGRC review.** The MAJCOM/SGP or ANGRC/SGP will review the centrifuge training reports and recommendations and the medical evaluation report, and they may review the aircrew's centrifuge training videotapes (if desired). Based on the medical and physiological review, the MAJCOM/SGP or ANGRC/SGP will provide a recommendation to the MAJCOM/DOT/XOT or ANGRC/DOT as to the aircrew's potential to tolerate the high-G environment. The MAJCOM/DOT/XOT or ANGRC/DOT will review the operations group commander and MAJCOM/SGP or ANGRC/SGP recommendations and prepare a consolidated position to the MAJCOM/DO/XO or ANGRC/DO. The MAJCOM/DO/XO or ANGRC/DO is the final authority in determining whether the aircrew is retained in their weapon system, whether approved to continue conversion, or if the aircrew should be reassigned to a low-G weapon system.

2.4. Waiver Procedures. Waiver requests must be by name and submitted in writing with appropriate justification through the NAF/DO to the MAJCOM/DO/XO. NAF will screen requests and recommend concurrence or nonconcurrence to the MAJCOM/DO/XO. All requests for waivers for the ANG will be submitted directly to the ANGRC/DO. The MAJCOM/DO/XO or ANGRC/DO is the final waiver authority.

2.4.1. Waivers to initial training will be considered for the following circumstances:

2.4.1.1. Unit is converting from low-G to high-G aircraft and aircrew will not convert.

2.4.1.2. Aircrew is separating from the Air Force or retiring within 90 days (6 months for ANG aircrew) of when the aircrew would otherwise be required to attend training.

2.4.1.3. Aircrew failed initial and retraining, but was recommended to continue in HGA (paragraph 2.3.2.5.). An approved waiver to the training requirement also constitutes a waiver to the formal course entry prerequisite for aircrews who are enrolled in or en route to a formal training course.

2.4.2. Waivers to modify (reduce) the centrifuge profiles will only be reviewed for aircrews on current medical waivers. Cases will be reviewed individually by the MAJCOM/SGP or ANGRC/SGP, who will then provide a recommendation to the MAJCOM/DOT/XOT or ANGRC/DOT. The MAJCOM/DOT/XOT or ANGRC/DOT prepares the recommendation for the MAJCOM/DO/XO or ANGRC/DO. The MAJCOM/DO/XO or ANGRC/DO is the final approval authority for modifying centrifuge profiles.

Chapter 3

REFRESHER TRAINING

3.1. Overview. Refresher training is designed for aircrews who are being reassigned to high-G aircraft following a nonflying assignment or who are converting from an LGOR aircraft to a HGOR aircraft. Refresher training is also available for aircrews with demonstrated low-G tolerance. All training is conducted at an authorized centrifuge training facility and consists of both academic instruction and spin profiles. Prior HQ ACC/SGP approval is required for training at Brooks AFB, Texas.

3.2. Applicability. Senior officers (O-6 select and above), once trained under either the initial or refresher program (as appropriate), do not require further training unless specifically directed by MAJCOM/DO/XO or ANGRC/DO. General officers who are authorized to fly solo (regardless of major defense system) or who fly with a pure single-seat HGA unit require one-time training under reason paragraph 3.2.1. General officers who are authorized to fly only with an instructor pilot in the same aircraft are exempt from training. Refresher training is required under the following circumstances:

3.2.1. All experienced rated officers who have not previously completed initial training. These aircrew attend refresher in place of initial training.

3.2.2. Aircrews returning to HGA from 3 or more years in a nonflying position or converting to a HGOR aircraft from 3 or more years in a LGOR. The 3 years are counted from the last flight as an active high-G aircrew in a HGOR aircraft (or since last completing centrifuge training) to formal course entry date (report-not-later-than date for aircrews who won't attend a formal course en route to their gaining unit).

3.2.3. Aircrews on MAJCOM and ANGRC waivers for failure of initial training (paragraph 2.4.1.3) require refresher training every 3 years. Aircrews in this category may, with prior flight surgeon concurrence, elect to reattempt initial training profiles vice refresher training profiles. Once initial training profiles are successfully completed, the aircrew's AF Form 702 will be documented accordingly; the waiver will be rescinded; and no further refresher training will be required (unless directed by paragraphs 3.2.2, 3.2.4, or 3.2.5).

3.2.4. Following an inflight GLOC incident.

3.2.5. When directed by the commander to improve aircrew performance under Gs.

NOTE: Aircrews attending training for reasons of paragraphs 3.2.1 or 3.2.2 must attend training prior to their formal course entry date, if applicable, and they must pass the refresher training program or receive a MAJCOM/DO/XO or ANGRC/DO waiver.

3.3. Requirements. Completion of all training prescribed by this section is required; except, in event of an equipment malfunction, training may be completed without profiles 3 or 4. Only a qualified aerospace physiologist (reference AFI 11-403) is authorized to document centrifuge training completion on the AF Form 702. Documentation will reflect "AFI 11-404 centrifuge refresher training complete" or "AFI 11-404 initial centrifuge training complete," as appropriate. Training consists of the following:

3.3.1. **Platform Academic Instruction.** Minimum 2 hours of platform academic instruction covering the effects of acceleration forces on mobility and respiration, characteristics of GLOC, techniques of an effective AGSM, and protection offered by current and future anti-G systems. Also, included will be an interactive discussion of the impact of physical conditioning, lifestyle, and proper nutrition on individual G-tolerance and on the effectiveness of the AGSM. "There I was" discussions are encouraged.

3.3.2. **Four Centrifuge Profiles.** Aircrews currently flying or converting to the F-16 (or any future aircraft with a reclined seat) will train in the 30-degree reclined seat. All other aircrews will train in the 13-degree straight-up seat. All profiles will be videotaped. Aircrews may request training up to 7.5 Gs (9 Gs reclined seat), but performance beyond the minimum levels listed is not evaluated for completion requirements. The following are refresher training profiles and will be accomplished in the order listed:

3.3.2.1. **First profile.** Gradual onset run to 15 seconds beyond relaxed G-tolerance or to second peripheral light loss, whichever occurs first. The purpose of this run is to determine the aircrew's resting G-tolerance (established by first peripheral light loss while relaxed or prior to initiation of AGSM) and then to determine the effectiveness of the AGSM. The G-suit is not functional for this run.

3.3.2.2. **Second profile.** Rapid onset run to 1 G above resting tolerance, but not less than 6 Gs, for 20 seconds. The purpose of this run is to practice the proper AGSM. The G-suit is connected for this and all subsequent runs. Satisfactory completion of this profile is mandatory to complete training. If performance is not satisfactory, the aircrew may request another practice of the first profile, then reattempt the second profile.

3.3.2.3. **Third profile.** Rapid onset run to 1 G above resting tolerance for 10 seconds during "Check 6" position

(looking over left shoulder). Although the goal is to maintain max G for 10 seconds.

3.3.2.4. **Fourth profile.** Simulated air combat mission; the aircrew tracks a target through a series of maneuvers at a 3 G minimum and 7 G maximum (8 Gs reclined seat).

3.3.3. **Debrief.** Aircrews will receive a verbal debrief following each profile, with emphasis on improving the aircrew's AGSM. The overall debrief will include a review of the aircrew's videotape with emphasis on the AGSM and, if warranted, a written recommendation to the aircrew for a tailored conditioning program designed to increase the individual's potential G-tolerance. This recommended program will include lifestyle and physical conditioning comments as appropriate.

3.4. Noncompletion of Training. If training is incomplete due to factors beyond the aircrew's control, no actions are required beyond rescheduling of training. Recommendation for non-completion due to aircrew performance is made by the aerospace physiologist who monitored the individual's training. The training facility chief is the final authority for determining non-completion. Once this recommendation is validated, the procedures in this section will be implemented.

3.4.1. **Notification.** The centrifuge facility chief will notify the aircrew's commander in writing of the failure and provide a copy of the aircrew's training report and the tailored conditioning program recommended in the debrief. For aircrews en route to an FTU, this notification is sent to the FTU squadron commander. MAJCOM or ANGRC notification is required only for aircrews who attended due to reasons in paragraphs 3.2.1, 3.2.2, or 3.2.3.

3.4.2. **Grounding.** Aircrews are not medically grounded following refresher training beyond the 12-hour automatic DNIF.

3.4.3. **Restrictions.** There is no automatic restriction following failure of refresher training. Following a review of the centrifuge training record and consultation with the flight surgeon and the centrifuge facility chief, the squadron commander may restrict pilot aircrews from solo high-G operations until successful completion of an operational review (if required).

3.4.4. **Conditioning Program.** The aircrew's commander or commander-designated representative will monitor the aircrew's progress in the conditioning program. The aircrew must be afforded sufficient opportunity (minimum 3 times per week) to work on their individual conditioning program. Aircrews who have weight training recommended as part of this program should seek professional assistance in establishing their program. When diet or lifestyle changes are recommended, the aircrew should seek appropriate assistance from the unit medical group or other base agencies.

3.4.5. **Operational Review.** An operational review is only required for aircrew who attended refresher training for reason 3.2.2., except it is not required for experienced rated officers. See paragraph 2.3.2.4 for operational review procedures.

3.4.6. **MAJCOM or ANGRC Review.** A MAJCOM or ANGRC review is required following all operational reviews. See paragraph 2.3.2.5 for operational review procedures.

3.5. Waiver Procedures. Waiver requests must be by name and submitted in writing, with appropriate justification, through the NAF/DO to the MAJCOM/DO/XO. The NAF will screen requests and recommend concurrence or non-concurrence to the MAJCOM/DO/XO. All requests for waivers for the ANG will be submitted directly to the ANGRC/DO. The MAJCOM/DO/XO or ANGRC/DO is the final waiver authority.

3.5.1. Waivers to refresher training will be considered for the following circumstances:

- Experienced rated officer who was unable to complete training.
- Other aircrews who attended training that was not in conjunction with conversion to a high-G aircraft.
- Aircrews recommended to continue in HGA following their operational review.

3.5.2. An approved waiver to the refresher training requirement also constitutes a waiver to the formal course entry prerequisite for aircrews who are enrolled in or en route to a formal training course.

3.5.3. Aircrews on approved refresher training waivers do not require further centrifuge training except as **directed** by paragraph 3.2.4. or 3.2.5.

Chapter 4

REPORTING

4.1. Overview. Completion of centrifuge training is documented on the AF Form 702 as described in this instruction. Notification of non-completion is also accomplished according to this instruction. The centrifuge training facility will provide an end-of-calendar year report to its MAJCOM/DO/XO and SG which delineates the following (with anonymity):

4.1.1. Number of persons (by aircrew mission, design, series (MDS) and position) who attended training by a training program (initial or refresher). For refresher

training, list reason for attendance separately if known (paragraph 3.2).
4.1.2. Number of failures and rate by training program, MDS, and position. Consolidate reasons for failures and provide separate list with rates (e.g. GLOC--10 percent, inadequate AGSM--75 percent, poor physical condition--20 percent, etc.).
4.1.3. Injuries or medical problems, in association with training, by aircrew MDS and age.
4.1.4. Synopsis of critique comments. Only include comments directed at the overall program or policies. Comments on the facility or its personnel need not be sent forward.
4.1.5. Specific comments or recommendations by the facility chief regarding program policy or procedures.

4.2. Videotape Disposition. The videotapes of aircrew centrifuge training are controlled items. The centrifuge training facility will maintain original videotapes by according to AFI 37-133, volume 2, *Disposition of Air Force Records--Records Disposition Schedule.* Only the MAJCOM/SG (ANGRC/SG for ANG aircrew) is authorized to release videotapes outside the MAJCOM/SGP or ANGRC/SGP. The centrifuge facility will copy only the training profiles for the individual aircrew requested by the MAJCOM/SG or ANGRC/SG. This copy will be labeled "for official use only" and afforded protection from unauthorized disclosure.

4.3. Individual Records. Units will track initial centrifuge training via AFORMS and in individual flight records. Aircrews will be identified as: initial training required, initial training complete, or MAJCOM/ANGRC waiver. Aircrew records should be screened annually to determine when the aircrew, if any, on waivers will require refresher training. Units will also develop a method to track refresher training attendance and completion.

4.3.1. The centrifuge training facility will maintain individual aircrew training records according to AFI 37-133, volume 2. This will serve as a back-up to unit records.

4.3.2. The training reports maintained by the centrifuge facility may be released to the aircrew's commander, MAJCOM/DOT/XOT, or MAJCOM/SGP (ANGRC/DOT/SGP for ANG aircrew). Requests for release of individual training reports to other agencies must be approved by the MAJCOM/DOT/XOT or ANGRC/DOT. These reports are "for official use only" and afforded protection from unauthorized disclosure.

4.4. Unit Reporting Requirements *(not applicable to ANG units).* Units will provide a "snapshot" report to the MAJCOM/DOT/XOT at the end of each training cycle, which delineates the total aircrew assigned, number who still require training and their status, and the number on MAJCOM waivers with their status. This report will be sent via message (or electronically) and is due not later than the last day of January or July following the training cycle covered by the report.

Chapter 5

MAJOR COMMAND (MAJCOM) TRAINING PROCEDURES

MAJCOM Supplements. Each MAJCOM may use this chapter to supplement (delete, change, or insert) the basic instruction with its unique training procedures. Send copies of the published chapters and combined instructions to all participating MAJCOMs. MAJCOMs may choose to incorporate their unique procedures into the basic and publish as one document, using one of the following methods:

- Publish the chapter along with the basic instruction as one document, or
- Paragraph supplementation within the basic. If this method is used, MAJCOMs will preface supplemental information with the MAJCOM acronym. For example:

5.1.1. **Waivers.**
5.1.2. **ACC Waivers.**

EDWIN E. TENOSO, Maj General, USAF
DCS/Plans and Operations

Lisinopril Study Group
G Tolerance Testing Protocols

NAME		SSAN	CASE NUMBER
DATE OF BIRTH	GRADE	AIRCRAFT	DATE

MEDICAL EVALUATION PROFILES						
Protocol Run	**Run Type (Onset Rate)**	**Max G Level**	**Duration Goal (sec)**	**Duration (sec)**	**Strain Goal**	**Termination (Comments)**
GOR1	01 (0.1 G/sec)				Relaxed	
*GORS	01 (0.1 G/sec)				Relaxed	
STANDARD AND TRAINING PROFILES						
Protocol Run	**Run Type (Onset Rate)**	**Max G Level**	**Duration Goal (sec)**	**Duration (sec)**	**Strain Goal**	**Termination (Comments)**
Training (warm-up)	08 (6 G/sec)	3.0	30		L-1	
Training (warm-up)	08 (6 G/sec)	5.0	15		L-1	
Training (warm-up)	08 (6 G/sec)	7.0	15		L-1	
Standard	08 (6 G/sec)	7.5	15	PASS/FAIL	L-1	

A fitted G-suit will be worn for all runs, G-suit will be connected to the regulator for only the Standard and Training Profiles.

GOR1 and GORS may be accomplished during the same run.

All training runs are to be performed and are for the purpose of establishing a good anti-G strain prior to the standard run.

The order of the runs can be adjusted to accommodate the aviator.

PVCs, PACs or other _____. Motion Sickness_____

MEDICAL MONITOR'S SIGNATURE	PRINTED NAME OR STAMP

9 Sep 96

MEMORANDUM FOR LTC COURTNEY SCOTT
HQ AFMOA/SGPA
170 Luke Ave, Ste 400
Bolling AFB, DC 20332-5113

FROM: AL/AOCI
2507 Kennedy Circle
Brooks AFB, TX 78235-5117

SUBJECT: Military Aviator Coronary Angiography Decision Equation

1. The positive predictive value of any test is influenced primarily by its specificity, and by the prevalence of the condition sought in the population being evaluated. Consequently, screening for coronary artery disease in a relatively low risk asymptomatic population, such as military aviators, results in a higher percentage of false positive tests than is typical of a symptomatic clinical population. Risk stratification improves this percentage; for instance, the positive predictive value of an abnormal exercise tolerance test (ETT) was 10% in unscreened USAF aviators, compared to 25% in aviators with abnormal resting ST-T wave changes.[1] However, in a later study of a similar population, sensitivity was poor, in that ETT alone missed at least 47% of SCAD.[2] Using thallium scintigraphy, Schwartz et al found a positive predictive value in detecting significant coronary artery disease (SCAD) of 25% when used to evaluate aviators referred to the Aeromedical Consult Service (ACS) for cardiac diagnoses. While such referral leads to some risk stratification by itself, further stratification of that group by age and cholesterol ratio yielded a positive predictive value of 41-43% in the highest risk groups. However, if angiography had only been performed on these high risk groups, at least 35% of SCAD would have been missed.[3] Coronary artery fluoroscopy (CAF) shows a similar sensitivity and a better positive predictive value for detecting SCAD in military aviators, and has the advantage of detecting minimal coronary artery disease (MCAD) as well. Evaluating aviators stratified only by referral to the ACS for cardiac evaluation, Loecker et al found a positive predictive value for fluoroscopy of 38% for SCAD, and 69% for all gradable CAD. However, using fluoroscopy alone would still have resulted in missing at least 34% of SCAD and 39% of gradable disease.[2]

2. Because of the relatively poor sensitivity of any one noninvasive test, the ACS has considered that any abnormal noninvasive study in a male aviator over 35 years of age required angiography to rule out coronary disease before waiver would be favorably considered. Since coronary angiography was rarely required in those with normal noninvasive tests, the true sensitivity of this method cannot be calculated, but positive predictive value has averaged approximately 35%. We surmised that application of an equation utilizing risk factors and results of noninvasive testing might allow fewer caths and a better positive predictive value, while still preserving sensitivity.

3. In the initial retrospective portion of this study, we reviewed records from 818 male aviators who were seen at the Aeromedical Consult Service from November 1982 to February 1993, and underwent

initial catheterization to rule out coronary disease. Extensive historical and laboratory data were available in each case, and included such recognized risk factors as age, history of hypertension, family history of premature coronary artery disease, smoking history, total cholesterol, HDL, and calculated LDL. In addition, all aviators underwent noninvasive screening for coronary disease, consisting of coronary fluoroscopy, treadmill exercise testing, and thallium scintigraphy. In all cases, the indication for coronary angiography consisted of an abnormal result from one or more noninvasive studies. Aviators undergoing catheterization for left bundle branch block or solely for arrhythmias were excluded from this study. Of the 818 aviators evaluated, 519 (63%) had normal coronary arteries, while 299 (37%) had gradable CAD. Of these, 156 (19%) had MCAD, defined for aeromedical purposes as a maximal stenosis less than 50%, with aggregate stenoses of less than 120%. Significant coronary artery disease, defined as a maximal stenosis of 50% or greater and/or an aggregate of 120% or more, was present in the remaining 143 (17%). Risk factor data and results of noninvasive testing were correlated with the results of coronary angiography. Using logistic regression, equations were developed for the "risk" of CAD. Initially, separate MCAD and SCAD risk equations were derived. As one would expect, the SCAD equation performed somewhat better in risk stratifying significant disease; since it also performed nearly as well as the MCAD equation for minimal disease, we simplified the decision process by applying the SCAD equation only. The formula for the equation is

$$\text{Risk} = 1 / 1 + e - (-8.07 + 2.09F + 0.97Th + 0.29R + 0.69Tr + 0.062A + 0.63S + 0.94FH + 0.77HT),$$

where

F = cardiac fluoroscopy,
Th = thallium,
R = cholesterol/HDL ratio,
Tr = treadmill,
A = age,
S = smoking history,
Fh = family history of premature coronary artery disease, and
HT = history of hypertension.

Smoking history is defined as any history of habitual smoking. Family history is defined per NCEP guidelines, as a history of coronary disease occurring before the age of 55 in a first degree male relative, or before the age of 65 in a first degree female relative. To answer whether the use of this equation could have avoided a significant number of caths while preserving sensitivity, results were calculated for each aviator and they were then rank ordered by increasing risk, with cath results annotated in a corresponding column. Selection of a threshold risk of 4.5% (i.e. cath would be required for a risk of SCAD greater than or equal to 4.5%) would have resulted in 20% fewer caths (655 instead of 818) while failing to identify only 2% (3/143) of documented SCAD cases and 6% (10/156) of documented MCAD cases. Thus the unadjusted sensitivity for detecting SCAD would have been 97.9%, and for detecting MCAD would have been 93.6%, with an unadjusted sensitivity for gradable disease of 95.7%. With 163 fewer caths, the positive predictive value would have risen from 36.6% to 43.7%. Setting the threshold risk higher than 4.5% resulted in a far more rapid rise of missed cases of disease compared with the number of catheterizations avoided.

4. It remained to be shown whether the risk equation derived from the earlier group of aviators could be applied against a subsequent group undergoing occupational evaluation. In order to prospectively validate the equation, SCAD risk was calculated for aviators undergoing initial catheterization at the ACS between February 1993 and August 1996. Indications were identical to the retrospective group, in that these were occupational evaluations to rule out coronary disease in the face of one or more abnormal

noninvasive tests. Of the 68 aviators, 50 (74%) had normal coronary arteries while 18 (26%) had gradable disease, 7 (10%) with SCAD and 11 (16%) with MCAD. Had the risk equation been applied using a 4.5% risk threshold, 16 (24%) fewer individuals would have undergone angiography; none of these proved to have gradable disease. In this group, then, unadjusted sensitivity would have remained at 100%, and positive predictive value would have risen from 26.5% to 36.4%.

5. Can we accept missing any coronary disease? There is background disease in any population, and even with an aggressive screening program, which the USAF does not have, some disease would be missed. Even in aviators referred to the ACS, hemodynamically insignificant stenoses which have not undergone dystrophic calcification would likely be missed by noninvasive testing. Furthermore, an aviator calculated to have a risk less than 4.5% by the decision equation would continue to have ACS follow-up; therefore, in the 4% of cases where disease was "missed," diagnosis would likely be delayed rather than missed entirely.

6. The ACS recommends that this equation be implemented to determine aeromedical disposition of an aviator with abnormal noninvasive testing. If calculated risk is less than 4.5%, unrestricted waiver would be recommended without requiring cardiac catheterization. ACS follow-up would be required every three years for that group. The risk equation would only be reapplied in the event of a newly abnormal noninvasive test, or a significant change in risk factors. Based on the prospective validation of this equation, we feel ethically obligated to implement this policy, and plan to do so 1 Oct 1996 unless you inform us differently.

JAMES W. SLAUSON, Maj, USAF, MC
Staff Internist, Internal Medicine Branch
Clinical Sciences Division

WILLIAM B. KRUYER, MD, FACC
Chief Cardiologist, Internal Medicine Branch
Clinical Sciences Division

JEB S. PICKARD, Col, USAF, MC, FS
Chief, Internal Medicine Branch
Clinical Sciences Division

1 Attachment
References

REFERENCES

1. Hickman JR. Noninvasive methods for the detection of coronary artery disease in aviators--a stratified Bayesian approach. Advisory Group for Aerospace Research and Development (AGARD). 1987; Report No 758:2-1 to 2-11.

2. Loecker TH, Schwartz RS, Cotta CW, Hickman JR. Fluoroscopic coronary artery calcification and associated coronary disease in asymptomatic young men. J Am Coll Cardiol 1992;19:1167-72.

3. Schwartz RS, Jackson WG, Celio PV, et al. Accuracy of exercise ^{201}Tl myocardial scintigraphy in asymptomatic young men. Circulation 1993;87:165-72.

1. With the completion of the Lisinopril Study Group and an evaluation of the data, hypertensive aviators treated with lisinopril are no longer required to undergo initial evaluation at the ACS. Instead they will have a local evaluation with submission of a waiver request to the MAJCOM. The new algorithm approach for hypertensive aviators is included as attachment 1and is a direct result of the findings of the lisinopril study.

2. Initial evaluations for aviators placed on either diuretics or lisinopril should be summarized in a standard aeromedical summary and should include:

   a. A brief summary of the aviator's hypertension history including date and description of onset, initial diagnosis, how secondary causes were excluded, previous treatments and the effect including both pharmacologic and non-pharmacologic methods. If one medication was tried first and was unsuccessful, include reason for switching to an alternate drug. CAD risk factors need to be listed. Initial lab, and lab at the end of 30 days should be included in their entirety as well as results of all 5-day blood pressure averages. The aviator should be DNIF during this 30 day period. Any side effects from medication (or the lack thereof) should be noted. Final dosage of medication should be included. If done, please note results of audiometry and eye examinations. A brief summary of physical exam findings should be noted as well. EKG, echo, and CXR results should be noted. EKG and echo results along with echo tape need to be sent to the ACS EKG Library for reading.

   b. If the aviator is male and 40 or older, or female and 50 or older, a treadmill and coronary artery fluoroscopy need to be performed and results sent to the ACS. Treadmill tracings need to be sent as well. If either of these is positive, the aviator will need ACS evaluation for positive noninvasive tests. Hypertensive aviators less than age 40 if male, or less than age 50 if female, do not require this noninvasive screen for CAD until they reach the age of 40 (or 50 if female).

   c. For lisinopril only, if the aviator flies high performance aircraft, they will need to go to the ACS for centrifuge testing. If available, results from any previous centrifuge testing should be noted in the AMS. Try to schedule this as soon as possible once BP is controlled (DSN 240-3646).

3. Annual re-evaluations for hypertension treated with medication should be documented on an AMS and include the following information:

   a. Brief interval history which notes any new side effects (or lack thereof), any change in dose, 5 day blood pressure average, and results of lab tests and ECG. If aviator had been evaluated at the ACS in the past, please note this along with a brief summary of the ACS evaluation. The results of any additional local testing should be included.

   b. If high performance, report any effects (or lack thereof) on G tolerance noted by the pilot or by the flight surgeon on G-tape review.

   c. Any additional waivers or medical conditions should be noted, especially if new.

   d. Waivers granted for three years are contingent upon this annual submission.

   e. Echo, treadmill and fluoroscopy should be repeated every 5 years if initial testing is negative. Positive tests will have re-evaluation intervals dictated by established policies dependent on the diagnosis resulting from the positive test.

4. A copy of the AMS for both initial and re-evaluations should be sent to the MAJCOM as well as the ACS so that hypertension in aviators can continue to be tracked.

5. Aviators with an elevated 5-day blood pressure who are treated with a non-pharmacologic approach (i.e., diet and exercise) will also require a waiver for "Mild Hypertension treated with diet and exercise". An AMS relating the pertinent findings from the history and physical as well as CAD risk factor information should be submitted to the local 48A-3, who is the waiver authority for this diagnosis. A copy of the AMS should go to the MAJCOM for tracking. MAJCOMs need to keep this waiver information current in the waiver file so that the ACS can track this diagnosis Air Force wide. These aviators need to be followed monthly by their flight surgeon with blood pressure checks, and with a five-day blood pressure average at the end of the six-month trial. There is no DNIF with this diagnosis.

6. For those interested, a copy of the Technical Report listing the findings of the lisinopril study group, including the reasons for the new approach to the treatment of aviators with hypertension, will be posted on the ACS website (www address)